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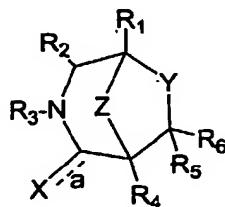
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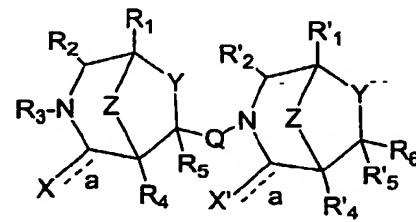
- with international search report
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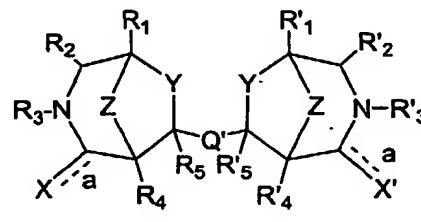
(54) Title: PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF DISEASES RELATED TO NEUROTROPHINES



(I)



(II)



(III)

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(57) Abstract: The present invention refers to pharmaceutical preparations including as active compounds 3-aza-bicyclo[3.2.1]octane derivatives of general formula (I) and/or their dimers of general formula (II) and (III) acting as agonists of human neurotrophines. Therefore, such compounds of formula (I), (II) and (III) are useful for treatment of diseases in which the neurotrophine functions are involved in defect, particularly of Nerve Growth Factor (NGF), such as neurodegenerative diseases of central nervous system (CNS), acquired immunodeficiency due to a reduced NGF biodisponibility, or morbus conditions in which the stimulus of neoangiogenesis process is convenient.

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 3519PTWO/1a	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 03/ 06471	International filing date (day/month/year) 18/06/2003	(Earliest) Priority Date (day/month/year) 19/06/2002
Applicant GUARNA, Antonio		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :

contained in the international application in written form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. Certain claims were found unsearchable (See Box I).

3. Unity of invention is lacking (see Box II).

4. With regard to the title,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF DISEASES RELATED TO
NEUROTROPHINES

5. With regard to the abstract,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

as suggested by the applicant.

because the applicant failed to suggest a figure.

because this figure better characterizes the invention.

None of the figures.

PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF DISEASES RELATED TO NEUROTROPHINES

FIELD OF THE INVENTION

5 The present invention refers to pharmaceutical compositions comprising 3-aza-bicyclo[3.2.1]octane derivatives of general formula (I), their dimers of general formula (II) or (III) hereinäfter reported, or mixtures thereof, useful in the treatment of pathologies in which the neurotrophine functions, particularly of Nerve Growth Factor (NGF), are altered.

10 STATE OF THE ART

Numerous proteins and polypeptidic factors regulate cell growth and/or survival. The first of such factors which was identified and functionally characterised is NGF. Later on, other proteins belonging to the same NGF family were identified that exert their activity on different populations of nervous cells. All these proteins 15 are collectively referred to as "neurotrophins".

NGF, upon interaction with specific surface receptors, prevents neuronal cell death during embryonal development and throughout adult life. NGF administration was proven advantageous in pathological conditions, such as degenerative and ischaemic disorders of Central Nervous System (CNS), spinal lesions, and toxicity 20 of excitatory amino acids. In fact, together with other neurotrophic factors, NGF promotes neuronal regeneration and supports neuronal functions.

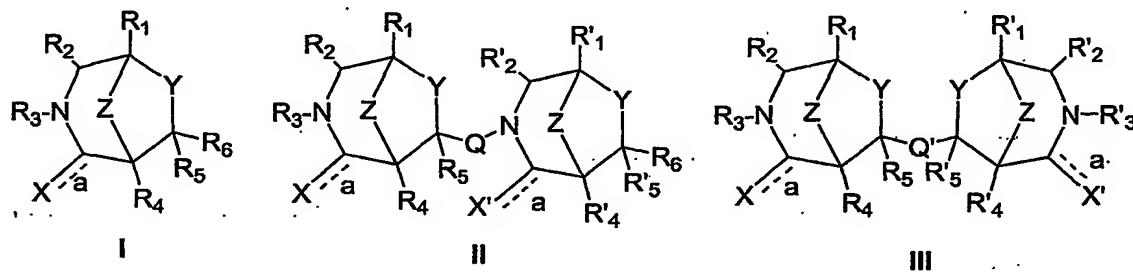
Therapeutic uses of NGF have been limited by its poor ability to get across the blood-brain-barrier, partly due to the molecular size of the native factor. Thus, the development of non-peptidic compounds able to specifically mimic the activities of 25 the natural ligand is a useful approach to obviate such limitations. Relevant examples of such compounds are: a) phorbol esters, that mimic NGF presumably by modifying PKC α activity; b) ganglioside and other unrelated lipidic compounds, that promote neuritic outgrowth from dorsal root ganglia, or other sympathetic, neurones; c) Triap (1,1,3-triciano-2-ammino-1-propene), a small compound able to 30 support survival and induce neuritic growth in PC12 cells. In all of the above cases, activity of molecules is not mediated by interactions with NGF receptors. Development of new non-peptidic compounds able to interact with specific

receptors, thus behaving as agonists or antagonists, of human neurotrophins is of utmost importance, since they may be used as drugs for treatment of disorders related to a defective or excessive activity of neurotrophins.

SUMMARY OF THE INVENTION

Now, the Applicants have unexpectedly found that 3-aza-bicyclo[3.2.1]octane derivatives of general formula (I) and their dimers of general formula (II) and (III) as reported hereinafter, are active as agonists of human neurotrophines, therefore they are useful for preparation of pharmaceutical compositions for the treatment of diseases in which the neurotrophine functions, particularly the NGF functions, are involved in defect.

It is therefore subject of the present invention a pharmaceutical composition comprising as the active principle at least one among the 3-aza-bicyclo[3.2.1]octane derivatives of general formula (I), or their dimers of general formula (II) and (III), or mixtures thereof:



wherein:

R_1 and R'_1 , equal or different between each other, are selected from the group consisting of H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, cycloalkyl, aryl, heterocycle, aryl C_{1-8} alkyl; heterocycle C_{1-8} alkyl, $RR'N-C_{1-8}$ alkyl, $RR'N$ -aryl, FmocNR'-aryl, BocNR'-aryl, CBzNR'-aryl, RO-aryl, $R(O)C$ -aryl, $RO(O)C$ -aryl, $RR'N(O)C$ -aryl; FmocNR'- C_{1-8} alkyl, BocNR'- C_{1-8} alkyl, CbzNR'- C_{1-8} alkyl, FmocNR'- C_{1-8} aryl, BocNR'- C_{1-8} aryl and CbzNR'- C_{1-8} aryl,

R_2 and R'_2 , equal or different between each other, are selected from the group consisting of H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, cycloalkyl, aryl, aryl C_{1-8} alkyl, heterocycle C_{1-8} alkyl, amino C_{1-8} alkyl, aminoaryl, C_{1-8} alkyloxyaryl, hydroxyaryl, hydroxy C_{1-8} alkyl, carboxy C_{1-8} alkyl, methyloxycarbonyl C_{1-8} alkyl, carboxyaryl, carboalkyloxyaryl, alkylcarbamoylaryl and -(side chains of amino acids), or

R_1 and R_2 , taken together, and R_1' and R_2' , taken together, are C_{1-4} alkyl, C_{2-4} alkenyl, cycloalkyl or benzofused cycloalkyl, to form a bridge of 3, 4, 5, 6 terms,

R_3 and R_3' are selected from the group consisting of H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, cycloalkyl, aryl, arylC₁₋₈alkyl, heterocycleC₁₋₈alkyl, RR'NC₁₋₈alkyl,

5 RR'Naryl, RO-C₁₋₈alkyl, RO(O)C-C₁₋₈alkyl, R(O)C-C₁₋₈alkyl, RC(O)O-C₁₋₈alkyl, RC(O)N(R)C₁₋₈alkyl, RO-aryl, RO(O)C-aryl, R(O)C-aryl RC(O)O-aryl, RC(O)N(R)aryl, -CH(amino acid side-chain)CO₂R, -CH(amino acid side-chain)C(O)NR, -CH(CO₂R)- amino acid side-chain, CH(CONRR')- amino acid side-chain, Fmoc, Boc and Cbz,

10 R_4 , R'_4 R_5 , and R'_5 , equal or different amongst each other, are selected from the group consisting of H, C_{1-8} alkyl, C_{2-8} alchenyl, C_{2-8} alchiny, cycloalkyl, aryl, heterocycle, arylC₁₋₈alkyl and heterocycleC₁₋₈alkyl,

R_6 is selected from the group consisting of H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, cycloalkyl, aryl, arylC₁₋₈alkyl, heterocycle, heterocycleC₁₋₈alkyl; -C(O)R, -C(O)OR, -

15 C(O)NRR', CH₂OR, CH₂NRR', -C(O)NH-CH(amino acid side-chain)C(O)OR, CH₂NR-Fmoc, CH₂NR-Boc and CH₂NR-Cbz,

R and R' , equal or different between each other, are selected from the group consisting of H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl; cycloalkyl, aryl, heterocycle, arylC₁₋₈alkyl; heterocycleC₁₋₈alkyl; protecting group, -C(O)CH-(amino acid side-chain)-NHT, -NH-CH(amino acid side-chain)COOT and -CH(amino acid side-chain)COOT,

20 where T is selected from between H and C_{1-8} alkyl;

X and X', equal or different between each other, are selected from between O and S, when a is a double bond, or

25 X and X' are both H, when a is a single bond,

Y and Z, equal or different from each other, are selected from the group consisting of O, S, SO, SO₂ and N-R, wherein R is as above defined;

Q is selected from the group consisting of C=O, CH₂, CO-NH-CH (amino-acid side-chain)-CO, CONR(CH₂)_nCO, CONR-C₂₋₈alkenyl-CO C(O)O(CH₂)_nCO,

30 CH₂OC(O)(CH₂)_nCO, and CH₂NRC(O)(CH₂)_nCO, wherein n is comprised between 2 and 6, and R is as above defined,

Q' is selected from the group consisting of C(O)OCH₂, C(O)NRCH₂, CH₂OC(O), CH₂NRC(O), CONR(CH₂)_nNRCO, CONR-C₂₋₈alkenyl-NRCO, C(O)O(CH₂)_nNRCO, CONR(CH₂)_nOC(O), CH₂OC(O)(CH₂)_nOC(O)CH₂, CH₂NRC(O)(CH₂)_nNRC(O)CH₂, CH₂OC(O)(CH₂)_nNRC(O)CH₂, CH₂NRC(O)(CH₂)_nOC(O)CH₂,

5 CH₂NR(CH₂)_nNRCH₂, CH₂O(CH₂)_nOCH₂, CH₂O(CH₂)_nNRCH₂, and CH₂NR(CH₂)_nOCH₂, wherein n is comprised between 2 and 6, and R is as above defined,

and where the groups alkyl, alkenyl, alkynyl, cycloalkyl, aryl and the heterocyclic groups above reported, are possibly substituted.

10 Further subject of the invention are the novel 3-aza-bicyclo[3.2.1]octane derivatives of general formula (I) and their dimers of general formula (II) and (III) above reported.

Further subject of the invention is the use of 3-aza-bicyclo[3.2.1]octane derivatives of general formula (I) and their dimers of general formula (II) and (III) above

15 reported for the preparation of pharmaceutical compositions useful for the treatment of:

20 i) neurodegenerative disorders of the Central Nervous System, such as Alzheimer Disease (AD), Amyotrophic Lateral Sclerosis (ALS), Huntington disease, neuropathies, neural damage caused by hypoxia, ischaemia, or trauma, inducing apoptosis of nervous cells;

ii) acquired immunodeficiency diseases related reduced bioavailability of NGF, such as immunodeficiency of ageing;

iii) diseases in which stimulation of neoangiogenesis turns out to be advantageous, such as myocardial infarction, stroke, or peripheral vasculopathies;

25 iv) certain pathologies of the eye, such keratitis of diverse aetiology, glaucoma, degenerative or inflammatory conditions of the retina.

Further subject of the invention is the use of 3-aza-bicyclo[3.2.1]octane derivatives of general formula (I), their dimers of general formula (II) or (III) above reported, and mixtures thereof, for the preparation of culture and storage media useful for 30 conservation of explanted corneas destined to transplantation, and the use for promoting *in vivo*, *in vitro*, or *ex vivo* growth and/or survival of neural cells.

Subject of the invention is also the use of 3-aza-bicyclo[3.2.1]octane derivatives of general formula (I), their dimers of general formula (II) or (III) above reported, and mixtures thereof, labelled with suitable reagents (contrast agents, radioisotopes, fluorescent agents etc.), and processed with any procedure useful for medical imaging purposes, for the imaging analysis of tissues and organs containing neurotrophine receptors, either *in vitro* or *in vivo*, in particular for monitoring the use and efficacy of drugs, as well as for the diagnosis of mammal diseases in which the neurotrophine receptors are involved.

5 The characteristic and advantages of the pharmaceutical compositions according to the invention will be in detail reported in the following description.

BRIEF DESCRIPTION OF THE DRAWINGS

10 Figure 1 shows the effect of present compounds on PC12 cell survival in serum-free conditions, by using hrNGF as internal standard according to paragraph "Biological Activity" hereinafter reported. Results were expressed as survival induced by compounds/spontaneous survival +100 for the compounds indicated on x axis.

15 Figure 2 shows the effect of present compounds on proliferative activity of PC3 cell line, in serum-free conditions, evaluated by using hrNGF as internal standard according to paragraph "Biological Activity". Results are expressed in terms of stimulation index, i.e. as ratio between ^3H -thymidine incorporation (mean \pm SD) of stimulated cultures and ^3H -thymidine incorporation of non stimulated cultures, for the compounds indicated on x axis.

20 Figure 3 illustrates the ability of present compounds (I), (II) and (III) to induce the VGF production by PC12 cells, evaluated as hereinafter described in paragraph "Biological Activity" in comparison with hrNGF. The control is 68 Kda VGF.

25 Figures 4a and 4b show the ability of present compounds to displace the ^{125}I -NGF binding to PC12 cells, by a displacement curve obtained by analysing the resultant cell bound radioactivity in the presence of the present compounds or in the presence of hrNGF with adequate software (Graphit 4) according to paragraph "Biological Activity".

30 Figure 4a shows the displacement curve obtained with the present compound 9 used as competitor. The analysis of data revealed a Kd of $165 \text{ nM} \pm 0.05$.

Figure 4b shows the displacement curve obtained by using hrNGF as competitor. The analysis of data revealed a K_d of $114 \text{ pM} \pm 0.01$.

Figure 5 shows the ability of the present compounds 272, 325, 9 and 91 to induce Trk-A autophosphorylation, by using hrNGF as internal standard according to 5 paragraph "Biological Activity".

Figure 6 shows the results obtained for the present compounds 9 and 325 and for the combination of the same two compounds, in a PC12 survival assay in serum-free condition, according to paragraph "Biological Activity". The results were expressed as survival induced by compounds/spontaneous survival $\times 100$.

10 DETAILED DESCRIPTION OF THE INVENTION

In the present invention by the expression "amino acid side chain" it is meant the side chain moieties of the natural occurring L or D amino acids or of the rare or non naturally occurring amino acids.

If it is not otherwise specified, the terms alkyl, alkenyl, alkynyl, aryl, arylalkyl, 15 cycloalkyl and heterocycle, as used in the present invention, should be meant as follows:

- C_{1-8} alkyl, C_{2-8} alkenyl and C_{2-8} alkynyl relate to linear or branched alkyl radicals, having only single bonds, at least one double bond, at least one triple bond respectively. Examples of alkylic groups according the present invention include

20 but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, heptyl, octyl. Examples of alkenyl groups, according to the present invention, include but are not limited to ethenyl, propenyl, 1-butenyl, cis-2-butenyl, trans-2-butenyl, 2-methyl-1-propenyl, 1-pentenyl, cis-2-pentenyl, trans-2-pentenyl, 2-methyl-2-but enyl. Examples of alkynyl groups according to the present invention include, 25 but are not limited to, ethynyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 3-methyl-1-butynyl;

- by the term "cycloalkyl" a ring containing carbon atom is meant, generally having from 3 to 8-members, and preferably from 5 to 6 members. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornanyl, canphanyl, adamantanyl;

- the term "aryl" indicates a group containing one or more unsaturated rings, each ring having from 5 to 8 members, preferably 5 or 6 members. Examples of aryl groups include, but are not limited to phenyl, biphenyl and naphthyl;

5 - the term "heterocycle" relates to saturated or aromatic heterocycles containing one or more heteroatoms, and preferably one or more N atoms. Examples of heterocycles include, but are not limited to pyridine, imidazole, pyrrole, indole, triazoles, pyrrolidine, pyperidine;

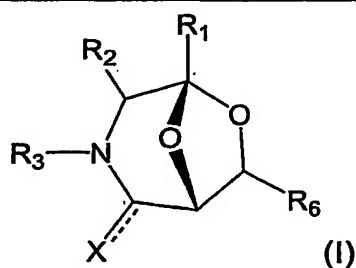
- the term "arylalkyl" indicates a group having an alkyl and an aryl substituent as above defined. As example, arylalkyl includes but is not limited to ethylphenyl, 10 isobutylphenyl, benzyl, ethylbenzyl, propylbenzyl, isopropylbenzyl, butylbenzyl, isobutylbenzyl, cyclohexylbenzyl, stirenyl and biphenyl.

In the present invention the groups fluorenylmethoxycarbonyl, t-butyloxycarbonyl, carboxybenzyl, benzyl, phenyl and acetyl are indicated using the common terms Fmoc, Boc, Cbz, Bn, Ph and Ac respectively.

15 Preferred are the present compounds of formula (I), (II) and (III) wherein Z is O. According to the present invention the alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heterocyclic groups may be substituted with one or more moieties, and preferably one or two moieties chosen from the group consisting of halogen, cyano, nitro, amino, hydroxy, carboxylic acid, carbonyl and C₁₋₆ alkyl. The term "halogen" 20 relates to fluorine, chlorine, bromine and iodine.

Among the compounds of general formula (I), (II) and (III) according the invention, the specific compounds reported in the following Tables 1-4 resulted of particular interest for their agonist activity against neurotrophines, and in particular of human NGF; and thus they are the compounds preferably used for the preparation of the 25 pharmaceutical compositions according to the invention.

Table 1



Compound	X	R ₁	R ₂	R ₃	R ₆
1	O	H	H	PhCH ₂	(R)-CO ₂ Me
2	O	H	H	PhCH ₂	(S)-CO ₂ Me
3	O	H	H	PhCH ₂	(R)-CON(CH ₂) ₅
4	O	H	H	PhCH ₂	(R)-CON(CH ₂) ₄
5	O	H	(S)-Me	PhCH ₂	(R)-CO ₂ Me
6	O	H	(S)-Me	PhCH ₂	(S)-CO ₂ Me
7	O	H	(R)-Me	PhCH ₂	(R)-CO ₂ Me
8	O	H	(R)-Me	PhCH ₂	(S)-CO ₂ Me
9	O	H	(R)-CH ₂ Ph	PhCH ₂	(S)-CO ₂ Me
10	O	H	(R)-CH ₂ Ph	PhCH ₂	(R)-CO ₂ Me
11	O	H	(S)-CH ₂ Ph	PhCH ₂	(S)-CO ₂ Me
12	O	H	(S)-CH ₂ Ph	PhCH ₂	(R)-CO ₂ Me
13	O	H	(S)-CH ₂ OBn	PhCH ₂	(R)-CO ₂ Me
14	O	H	(S)-CH ₂ OBn	PhCH ₂	(S)-CO ₂ Me
15	O	H	(R)-CH ₂ OBn	PhCH ₂	(R)-CO ₂ Me
16	O	H	(R)-CH ₂ OBn	PhCH ₂	(S)-CO ₂ Me
17	O	H	(S)-CH ₂ OH	PhCH ₂	(R)-CO ₂ Me
18	O	H	(S)-CH ₂ OH	PhCH ₂	(S)-CO ₂ Me
19	O	H	(R)-CH ₂ OH	PhCH ₂	(R)-CO ₂ Me
20	O	H	(R)-CH ₂ OH	PhCH ₂	(S)-CO ₂ Me
21	O	H	=CH ₂	PhCH ₂	(R)-CO ₂ Me
22	O	H	=CH ₂	PhCH ₂	(S)-CO ₂ Me
23	O	H	(R)-CH ₂ OH	PhCH ₂	(S)-CO ₂ Me
24	S	H	H	PhCH ₂	(R)-CO ₂ Me
25	S	H	H	PhCH ₂	(R)-CONH(CH ₂) ₂ NH ₂
26	S	H	H	PhCH ₂	(R)-CONH(CH ₂) ₂ OH
27	O	Ph	H	PhCH ₂	(R)-CO ₂ Me
28	O	Ph	H	PhCH ₂	(S)-CO ₂ Me
29	O	Ph	H	CH(Ph) ₂	(R)-CO ₂ Me
30	O	Ph	H	CH(Ph) ₂	(S)-CO ₂ Me

31	O	NO ₂ -Ph	H	Ph	(S)-CO ₂ Me
32	H	H	H	H	(R)-CO ₂ H
33	H	H	H	H	(S)-CO ₂ H
34	H	H	H	H	(R)-CO ₂ Me
35	H	H	H	H	(S)-CO ₂ Me
36	H	H	H	PhCH ₂	(R)-CO ₂ H
37	H	H	H	PhCH ₂	(S)-CO ₂ H
38	H	H	H	Fmoc	(R)-CO ₂ H
39	H	H	H	Fmoc	(S)-CO ₂ H
40	H	H	H	PhCH ₂	(R)-CO ₂ Me
41	H	H	H	PhCH ₂	(S)-CO ₂ Me
42	H	H	H	Boc	(R)-CO ₂ Me
43	H	H	H	Boc	(S)-CO ₂ Me
44	H	H	H	Fmoc	(R)-CO ₂ Me
45	H	H	H	Fmoc	(S)-CO ₂ Me
46	H	H	H	H	(R)-CONHMe
47	H	H	H	H	(S)-CONHMe
48	H	H	H	Ac	(R)-CONHMe
49	H	H	H	Ac	(S)-CONHMe
50	H	H	H	PhCH ₂	(R)-CONHMe
51	H	H	H	PhCH ₂	(S)-CONHMe
52	H	H	H	Fmoc	(R)-CONHMe
53	H	H	H	Fmoc	(S)-CONHMe
54	H	H	H	PhCH ₂	(R)-CON(CH ₂) ₅
55	H	H	H	PhCH ₂	(R)-CONHcyclohexyl
56	H	H	H	PhCH ₂	(R)-CON(CH ₂) ₄
57	H	H	H	PhCH ₂	(R)-CONH(CH ₂) ₂ OH
58	H	H	H	H	(R)-CH ₂ OH
59	H	H	H	H	(S)-CH ₂ OH
60	H	H	H	Fmoc	(S)-CH ₂ OH

61	H	H	H	Fmoc	(R) -CH ₂ OH
62	H	H	H	Boc	(R) -CH ₂ OH
63	H	H	H	Boc	(S) -CH ₂ OH
64	H	H	H	PhCH ₂	(R) -CH ₂ OH
65	H	H	H	PhCH ₂	(S) -CH ₂ OH
66	H	H	(S) -CH ₂ OBn	PhCH ₂	(R) -CO ₂ Me
67	H	H	(S) -CH ₂ OBn	PhCH ₂	(S) -CO ₂ Me
68	H	H	(R) -CH ₂ OBn	PhCH ₂	(R) -CO ₂ Me
69	H	H	(R) -CH ₂ OBn	PhCH ₂	(S) -CO ₂ Me
70	H	H	(S) -CH ₂ OBn	PhCH ₂	(R) -CH ₂ OH
71	H	H	(S) -CH ₂ OBn	PhCH ₂	(S) -CH ₂ OH
72	H	H	(R) -CH ₂ OBn	PhCH ₂	(R) -CH ₂ OH
73	H	H	(R) -CH ₂ OBn	PhCH ₂	(S) -CH ₂ OH
75	H	H	(S) -COOH	Fmoc	(R) -CO ₂ Me
76	H	H	(S) -COOH	Fmoc	(S) -CO ₂ Me
77	H	H	(R) -COOH	Fmoc	(R) -CO ₂ Me
78	H	H	(R) -COOH	Fmoc	(S) -CO ₂ Me
79	H	H	(S) -CH ₂ OBn	Fmoc	(R) -CO ₂ Me
80	H	H	(S) -CH ₂ OBn	Fmoc	(S) -CO ₂ Me
81	H	H	(R) -CH ₂ OBn	Fmoc	(R) -CO ₂ Me
82	H	H	(R) -CH ₂ OBn	Fmoc	(S) -CO ₂ Me
83	H	H	(S) -CH ₂ OBn	H	(R) -CO ₂ Me
84	H	H	(S) -CH ₂ OBn	H	(S) -CO ₂ Me
85	H	H	(R) -CH ₂ OBn	H	(R) -CO ₂ Me
86	H	H	(R) -CH ₂ OBn	H	(S) -CO ₂ Me
87	H	H	(S) -CH ₂ OH	H	(R) -CO ₂ Me
88	H	H	(S) -CH ₂ OH	H	(S) -CO ₂ Me
89	H	H	(R) -CH ₂ OH	H	(R) -CO ₂ Me
90	H	H	(R) -CH ₂ OH	H	(S) -CO ₂ Me
91	H	H	(S) -CH ₂ OH	Fmoc	(R) -CO ₂ Me
92	H	H	(S) -CH ₂ OH	Fmoc	(S) -CO ₂ Me

93	H	H	(R) -CH ₂ OH	Fmoc	(R) -CO ₂ Me
94	H	H	(R) -CH ₂ OH	Fmoc	(S) -CO ₂ Me
95	H	H	(S) -CH ₂ OH	Fmoc	(R) -CO ₂ Me
96	H	H	(S) -CH ₂ OH	Fmoc	(S) -CO ₂ Me
97	H	H	(R) -CH ₂ OH	Fmoc	(R) -CO ₂ Me
98	H	H	(R) -CH ₂ OH	Fmoc	(S) -CO ₂ Me
99	H	H	(S) -CH ₂ OH	PhCH ₂	(S) -CO ₂ Me
100	H	H	(R) -CH ₂ OH	PhCH ₂	(R) -CO ₂ Me
101	H	H	(R) -CH ₂ OH	PhCH ₂	(R) -CO ₂ Me
102	H	H	(R) -CH ₂ OH	PhCH ₂	(S) -CO ₂ Me
103	H	H	(S) -CH ₂ OH	Fmoc	(R) -CH ₂ OH
104	H	H	(S) -CH ₂ OH	Fmoc	(S) -CH ₂ OH
105	H	H	(R) -CH ₂ OH	Fmoc	(R) -CH ₂ OH
106	H	H	(R) -CH ₂ OH	Fmoc	(S) -CH ₂ OH
107	H	H	(S) -CH ₂ OH	PhCH ₂	(R) -CH ₂ OH
108	H	H	(S) -CH ₂ OH	PhCH ₂	(S) -CH ₂ OH
109	H	H	(R) -CH ₂ OH	PhCH ₂	(R) -CH ₂ OH
110	H	H	(R) -CH ₂ OH	PhCH ₂	(S) -CH ₂ OH
111	H	H	=CH ₂	PhCH ₂	(R) -CO ₂ Me
112	H	H	=CH ₂	PhCH ₂	(S) -CO ₂ Me
113	H	H	=CH ₂	PhCH ₂	(R) -CH ₂ OH
114	H	H	=CH ₂	PhCH ₂	(S) -CH ₂ OH
115	H	H	(S)-CH ₂ CH(Me) ₂	Fmoc	(R) -CH ₂ OH
116	H	H	(S)-CH ₂ CH(Me) ₂	PhCH ₂	(S) -CH ₂ OH
117	H	H	(S)-CH ₂ CH(Me) ₂	H	(R) -CH ₂ OH
118	H	Ph	H	H	(R) -CO ₂ Me
119	H	Ph	H	Fmoc	(R) -CO ₂ Me
120	H	Ph	H	PhCH ₂	(R) -CO ₂ Me
121	H	Ph	H	CH(Ph) ₂	(R) -CO ₂ Me
122	H	Ph	H	H	(S) -CO ₂ Me
123	H	Ph	H	Fmoc	(S) -CO ₂ Me

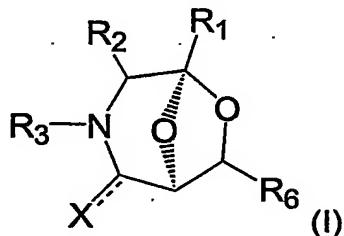
124	H	Ph	H	PhCH ₂	(S)-CO ₂ Me
125	H	Ph	H	CH(Ph) ₂	(S)-CO ₂ Me
126	H	p-NH ₂ -C ₆ H ₄	H	Ph	(S)-COOMe
127	H	p-NH ₂ -C ₆ H ₄	H	Ph	(S)-COOH
128	H	p-NH ₂ -C ₆ H ₄	H	Ph	(S)-CONHCH ₂ CO ₂ Me
129	H	p-NH-(Asp(O ^t Bu)-NH ₂)C ₆ H ₄	H	Ph	(S)-CO ₂ Me
130	H	p-NH-(Asp(O ^t Bu)NH ₂)-C ₆ H ₄	H	Ph	(S)-CO ₂ H
131	H	p-NH-(Asp(O ^t Bu)-NH ₂)C ₆ H ₄	H	Ph	(S)-CONH-Lys(NHBoc)-OMe
132	H	p-NH-(Asp(OH)-NH ₂)-C ₆ H ₄	H	Ph	(S)-CONH-Lys-OMe
133	H	p-NO ₂ -C ₆ H ₄	H	Ph	(S)-COOH
134	H	p-NO ₂ -C ₆ H ₄	H	Ph	(S)-COOMe
135	H	p-NO ₂ -C ₆ H ₄	H	Ph	(S)-CONHCH ₂ CO ₂ Me
136	H	Ph	H	H	(R)-CH ₂ OH
137	H	Ph	H	Fmoc	(R)-CH ₂ OH
138	H	Ph	H	PhCH ₂	(R)-CH ₂ OH
139	H	Ph	H	CH(Ph) ₂	(R)-CH ₂ OH
140	H	Ph	H	H	(S)-CH ₂ OH
141	H	Ph	H	Fmoc	(S)-CH ₂ OH
142	H	Ph	H	PhCH ₂	(S)-CH ₂ OH
143	H	Ph	H	CH(Ph) ₂	(S)-CH ₂ OH
144	H	H	(S)-Me	Fmoc	(R)-CO ₂ H
145	H	H	(S)-Me	Fmoc	(S)-CO ₂ H
146	H	H	(R)-Me	Fmoc	(R)-CO ₂ H

147	H	H	(R) -Me	Fmoc	(S) -CO ₂ H
148	H	H	(S) -Me	Fmoc	(R) -CO ₂ Me
149	H	H	(S) -Me	Fmoc	(S) -CO ₂ Me
150	H	H	(R) -Me	Fmoc	(R) -CO ₂ Me
151	H	H	(R) -Me	Fmoc	(S) -CO ₂ Me
152	H	H	(S) -Me	PhCH ₂	(R) -CO ₂ Me
153	H	H	(S) -Me	PhCH ₂	(S) -CO ₂ Me
154	H	H	(R) -Me	PhCH ₂	(R) -CO ₂ Me
155	H	H	(R) -Me	PhCH ₂	(S) -CO ₂ Me
156	H	H	(S) -Me	Fmoc	(R) -CH ₂ OH
157	H	H	(S) -Me	Fmoc	(S) -CH ₂ OH
158	H	H	(R) -Me	Fmoc	(R) -CH ₂ OH
159	H	H	(R) -Me	Fmoc	(S) -CH ₂ OH
160	H	H	(S) -Me	PhCH ₂	(R) -CH ₂ OH
161	H	H	(S) -Me	PhCH ₂	(S) -CH ₂ OH
162	H	H	(R) -Me	PhCH ₂	(R) -CH ₂ OH
163	H	H	(R) -Me	PhCH ₂	(S) -CH ₂ OH
164	H	H	(S) -PhCH ₂	Fmoc	(R) -CO ₂ H
165	H	H	(S) -PhCH ₂	Fmoc	(S) -CO ₂ H
166	H	H	(R) -PhCH ₂	Fmoc	(R) -CO ₂ H
167	H	H	(R) -PhCH ₂	Fmoc	(S) -CO ₂ H
168	H	H	(S) -PhCH ₂	Fmoc	(R) -CO ₂ Me
169	H	H	(S) -PhCH ₂	Fmoc	(S) -CO ₂ Me
170	H	H	(R) -PhCH ₂	Fmoc	(R) -CO ₂ Me
171	H	H	(R) -PhCH ₂	Fmoc	(S) -CO ₂ Me
172	H	H	(S) -PhCH ₂	PhCH ₂	(R) -CO ₂ Me
173	H	H	(S) -PhCH ₂	PhCH ₂	(S) -CO ₂ Me
174	H	H	(R) -PhCH ₂	PhCH ₂	(R) -CO ₂ Me
175	H	H	(R) -PhCH ₂	PhCH ₂	(S) -CO ₂ Me
176	H	H	(R) -PhCH ₂	H	(R) -CO ₂ Me
177	H	H	(R) -PhCH ₂	H	(S) -CO ₂ Me

178	H	H	(S) -PhCH ₂	H	(R) -CO ₂ Me
179	H	H	(S) -PhCH ₂	H	(S) -CO ₂ Me
180	H	H	(S) -PhCH ₂	Fmoc	(R) -CH ₂ OH
181	H	H	(S) -PhCH ₂	Fmoc	(S) -CH ₂ OH
182	H	H	(R) -PhCH ₂	Fmoc	(R) -CH ₂ OH
183	H	H	(R) -PhCH ₂	Fmoc	(S) -CH ₂ OH
184	H	H	(S) -PhCH ₂	PhCH ₂	(R) -CH ₂ OH
185	H	H	(S) -PhCH ₂	PhCH ₂	(S) -CH ₂ OH
186	H	H	(R) -PhCH ₂	PhCH ₂	(R) -CH ₂ OH
187	H	H	(R) -PhCH ₂	PhCH ₂	(S) -CH ₂ OH
188	H	H	(S)-PhCH ₂	PhCH ₂	(R)-COOH
189	O	p-NO ₂ Ph	H	Ph	CONH(CH ₂) ₆ NH ₂

Table 2

Compound	X	R ₁	R ₂	R ₃	R ₆
190	O	H	H	PhCH ₂	(R) -CO ₂ Me
191	O	H	H	PhCH ₂	(S) -CO ₂ Me
192	O	H	(S) -Me	PhCH ₂	(R) -CO ₂ Me
193	O	H	(S) -Me	PhCH ₂	(S) -CO ₂ Me
194	O	H	(R) -Me	PhCH ₂	(R) -CO ₂ Me
195	O	H	(R) -Me	PhCH ₂	(S) -CO ₂ Me
196	O	H	(S) -PhCH ₂	PhCH ₂	(R) -CO ₂ Me
197	O	H	(S) -PhCH ₂	PhCH ₂	(S) -CO ₂ Me
198	O	H	(R) -PhCH ₂	PhCH ₂	(R) -CO ₂ Me
199	O	H	(R) -PhCH ₂	PhCH ₂	(S) -CO ₂ Me
200	O	H	(S) -CH ₂ CH(Me) ₂	PhCH ₂	(R) -CO ₂ Me



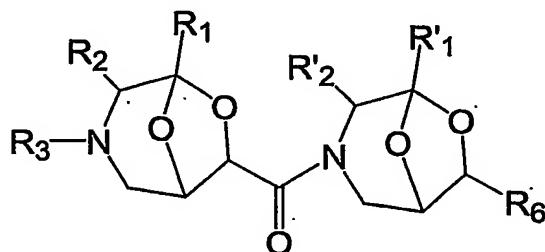
201	O	H	(S)-CH ₂ CH(Me) ₂	PhCH ₂	(S)-CO ₂ Me
202	O	H	(R)-CH ₂ CH(Me) ₂	PhCH ₂	(R)-CO ₂ Me
203	O	H	(R)-CH ₂ CH(Me) ₂	PhCH ₂	(S)-CO ₂ Me
204	O	H	H	PhCH ₂	(R)-CONHMe
205	O	H	H	PhCH ₂	(S)-CONHMe
206	O	H	(S)-Me	PhCH ₂	(R)-CONHMe
207	O	H	(S)-Me	PhCH ₂	(S)-CONHMe
208	O	H	(R)-Me	PhCH ₂	(R)-CONHMe
209	O	H	(R)-Me	PhCH ₂	(S)-CONHMe
210	O	H	(S)-PhCH ₂	PhCH ₂	(R)-CONHMe
211	O	H	(S)-PhCH ₂	PhCH ₂	(S)-CONHMe
212	O	H	(R)-PhCH ₂	PhCH ₂	(R)-CONHMe
213	O	H	(R)-PhCH ₂	PhCH ₂	(S)-CONHMe
214	O	H	(S)-CH ₂ CH(Me) ₂	PhCH ₂	(R)-CONHMe
215	O	H	(S)-CH ₂ CH(Me) ₂	PhCH ₂	(S)-CONHMe
216	O	H	(R)-CH ₂ CH(Me) ₂	PhCH ₂	(R)-CONHMe
217	O	H	(R)-CH ₂ CH(Me) ₂	PhCH ₂	(S)-CONHMe
218	H	H	H	Fmoc	(R)-CO ₂ H
219	H	H	H	Fmoc	(R)-CO ₂ Me
220	H	H	H	Fmoc	(S)-CO ₂ H
221	H	H	H	Fmoc	(S)-CO ₂ Me
222	H	H	(S)-Me	Fmoc	(R)-CO ₂ H
223	H	H	(S)-Me	Fmoc	(R)-CO ₂ Me
224	H	H	(S)-Me	PhCH ₂	(R)-CO ₂ Me
225	H	H	(R)-Me	Fmoc	(R)-CO ₂ H
226	H	H	(R)-Me	Fmoc	(R)-CO ₂ Me
227	H	H	(R)-Me	PhCH ₂	(R)-CO ₂ Me
228	H	H	(S)-Me	Fmoc	(S)-CO ₂ H
229	H	H	(S)-Me	Fmoc	(S)-CO ₂ Me
230	H	H	(S)-Me	PhCH ₂	(S)-CO ₂ Me
231	H	H	(R)-Me	Fmoc	(S)-CO ₂ H

232	H	H	(R)-Me	Fmoc	(S) -CO ₂ Me
233	H	H	(R)-Me	PhCH ₂	(S) -CO ₂ Me
234	H	H	(S)- PhCH ₂	Fmoc	(R) -CO ₂ H
235	H	H	(S)- PhCH ₂	Fmoc	(R) -CO ₂ Me
236	H	H	(S)- PhCH ₂	PhCH ₂	(R) -CO ₂ Me
237	H	H	(R)- PhCH ₂	Fmoc	(R) -CO ₂ H
238	H	H	(R)- PhCH ₂	Fmoc	(R) -CO ₂ Me
239	H	H	(R)- PhCH ₂	PhCH ₂	(R) -CO ₂ Me
240	H	H	(S)- PhCH ₂	Fmoc	(S) -CO ₂ H
241	H	H	(S)- PhCH ₂	Fmoc	(S) -CO ₂ Me
242	H	H	(S)- PhCH ₂	PhCH ₂	(S) -CO ₂ Me
243	H	H	(R)- PhCH ₂	Fmoc	(S) -CO ₂ H
244	H	H	(R)- PhCH ₂	Fmoc	(S) -CO ₂ Me
245	H	H	(R)- PhCH ₂	PhCH ₂	(S) -CO ₂ Me
246	H	H	(R)- CH ₂ OH	Fmoc	(S) -CO ₂ Me
247	H	H	(R)- CH ₂ OH	PhCH ₂	(S) -CO ₂ Me
248	H	H	(R)- CH ₂ OBn	Fmoc	(S) -CO ₂ Me
249	H	H	(R)- CH ₂ OBn	PhCH ₂	(S) -CO ₂ Me
250	H	H	(R)- CH ₂ OH	Fmoc	(R) -CO ₂ Me
251	H	H	(R)- CH ₂ OH	PhCH ₂	(R) -CO ₂ Me
252	H	H	(R)- CH ₂ OBn	Fmoc	(R) -CO ₂ Me
253	H	H	(R)- CH ₂ OBn	PhCH ₂	(R) -CO ₂ Me
254	H	H	(S)- CH ₂ OH	Fmoc	(S) -CO ₂ Me
255	H	H	(S)- CH ₂ OH	PhCH ₂	(S) -CO ₂ Me
256	H	H	(S)- CH ₂ OBn	Fmoc	(S) -CO ₂ Me
257	H	H	(S)- CH ₂ OBn	PhCH ₂	(S) -CO ₂ Me
258	H	H	(S)- CH ₂ OH	Fmoc	(R) -CO ₂ Me
259	H	H	(S)- CH ₂ OH	PhCH ₂	(R) -CO ₂ Me
260	H	H	(S)- CH ₂ OBn	Fmoc	(R) -CO ₂ Me
261	H	H	(S)- CH ₂ OBn	PhCH ₂	(R) -CO ₂ Me
262	H	H	(S)-CH ₂ CH(Me) ₂	Bn	(R) -CO ₂ Me

263	H	H	(R)-CH ₂ CH(Me) ₂	Bn	(R) -CO ₂ Me
264	H	H	(S)-CH ₂ CH(Me) ₂	Bn	(S) -CO ₂ Me
265	H	H	(R)-CH ₂ CH(Me) ₂	Bn	(S) -CO ₂ Me
266	H	H	(S)-CH ₂ CH(Me) ₂	Fmoc	(R) -CO ₂ Me
267	H	H	(R)-CH ₂ CH(Me) ₂	Fmoc	(R) -CO ₂ Me
268	H	H	(S)-CH ₂ CH(Me) ₂	Fmoc	(S) -CO ₂ Me
269	H	H	(R)-CH ₂ CH(Me) ₂	Fmoc	(S) -CO ₂ Me
270	H	H	(S)-Me	H	(R) -CH ₂ OH
271	H	H	(S)-Me	Bn	(R) -CH ₂ OH
272	H	H	(S)-Me	Fmoc	(R) -CH ₂ OH
273	H	H	(R)-Me	H	(R) -CH ₂ OH
274	H	H	(R)-Me	Bn	(R) -CH ₂ OH
275	H	H	(R)-Me	Fmoc	(R) -CH ₂ OH
276	H	H	(S)-Me	H	(S) -CH ₂ OH
277	H	H	(S)-Me	Bn	(S) -CH ₂ OH
278	H	H	(S)-Me	Fmoc	(S) -CH ₂ OH
279	H	H	(R)-Me	H	(S) -CH ₂ OH
280	H	H	(R)-Me	Bn	(S) -CH ₂ OH
281	H	H	(R)-Me	Fmoc	(S) -CH ₂ OH
282	H	H	(S)-CH ₂ CH(Me) ₂	H	(R) -CH ₂ OH
283	H	H	(S)-CH ₂ CH(Me) ₂	Bn	(R) -CH ₂ OH
284	H	H	(S)-CH ₂ CH(Me) ₂	Fmoc	(R) -CH ₂ OH
285	H	H	(R)-CH ₂ CH(Me) ₂	H	(R) -CH ₂ OH
286	H	H	(R)-CH ₂ CH(Me) ₂	Bn	(R) -CH ₂ OH
287	H	H	(R)-CH ₂ CH(Me) ₂	Fmoc	(R) -CH ₂ OH
288	H	H	(S)-CH ₂ CH(Me) ₂	H	(S) -CH ₂ OH
289	H	H	(S)-CH ₂ CH(Me) ₂	Bn	(S) -CH ₂ OH
290	H	H	(S)-CH ₂ CH(Me) ₂	Fmoc	(S) -CH ₂ OH
291	H	H	(R)-CH ₂ CH(Me) ₂	H	(S) -CH ₂ OH
292	H	H	(R)-CH ₂ CH(Me) ₂	Bn	(S) -CH ₂ OH
293	H	H	(R)-CH ₂ CH(Me) ₂	Fmoc	(S) -CH ₂ OH

294	H	H	(S)-PhCH ₂	H	(R)-CH ₂ OH
295	H	H	(S)-PhCH ₂	Bn	(R)-CH ₂ OH
296	H	H	(S)-PhCH ₂	Fmoc	(R)-CH ₂ OH
297	H	H	(R)-PhCH ₂	H	(R)-CH ₂ OH
298	H	H	(R)-PhCH ₂	Bn	(R)-CH ₂ OH
299	H	H	(R)-PhCH ₂	Fmoc	(R)-CH ₂ OH
300	H	H	(S)-PhCH ₂	H	(S)-CH ₂ OH
301	H	H	(S)-PhCH ₂	Bn	(S)-CH ₂ OH
302	H	H	(S)-PhCH ₂	Fmoc	(S)-CH ₂ OH
303	H	H	(R)-PhCH ₂	H	(S)-CH ₂ OH
304	H	H	(R)-PhCH ₂	Bn	(S)-CH ₂ OH
305	H	H	(R)-PhCH ₂	Fmoc	(S)-CH ₂ OH
306	H	H	(R)-CH ₂ OH	Fmoc	(S)-CH ₂ OH
307	H	H	(R)-CH ₂ OH	PhCH ₂	(S)-CH ₂ OH
308	H	H	(R)-CH ₂ OBn	Fmoc	(S)-CH ₂ OH
309	H	H	(R)-CH ₂ OBn	PhCH ₂	(S)-CH ₂ OH
310	H	H	(R)-CH ₂ OH	Fmoc	(R)-CH ₂ OH
311	H	H	(R)-CH ₂ OH	PhCH ₂	(R)-CH ₂ OH
312	H	H	(R)-CH ₂ OBn	Fmoc	(R)-CH ₂ OH
313	H	H	(R)-CH ₂ OBn	PhCH ₂	(R)-CH ₂ OH
314	H	H	(S)-CH ₂ OH	Fmoc	(S)-CH ₂ OH
315	H	H	(S)-CH ₂ OH	PhCH ₂	(S)-CH ₂ OH
316	H	H	(S)-CH ₂ OBn	Fmoc	(S)-CH ₂ OH
317	H	H	(S)-CH ₂ OBn	PhCH ₂	(S)-CH ₂ OH
318	H	H	(S)-CH ₂ OH	Fmoc	(R)-CH ₂ OH
319	H	H	(S)-CH ₂ OH	PhCH ₂	(R)-CH ₂ OH
320	H	H	(S)-CH ₂ OBn	Fmoc	(R)-CH ₂ OH
321	H	H	(S)-CH ₂ OBn	PhCH ₂	(R)-CH ₂ OH

Table 3



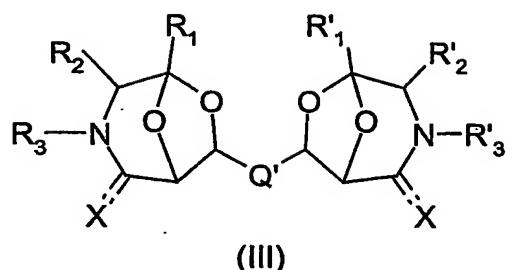
(II)

Compound	R ₁	R ₂	R ₃	R' ₁	R' ₂	R ₆
322	H	H	H	H	H	CO ₂ Me
323	H	H	H	H	H	CONHMe
324	H	H	PhCH ₂	H	H	CO ₂ Me
325	H	H	PhCH ₂	H	H	CONHMe
326	H	H	Fmoc	H	H	CO ₂ Me
327	H	H	Fmoc	H	H	CONHMe
328	H	H	Boc	H	H	CO ₂ Me
329	H	H	Boc	H	H	CONHMe
330	H	PhCH ₂	H	H	H	CO ₂ Me
331	H	PhCH ₂	H	H	H	CONHMe
332	H	PhCH ₂	PhCH ₂	H	H	CO ₂ Me
333	H	PhCH ₂	PhCH ₂	H	H	CONHMe
334	H	PhCH ₂	Fmoc	H	H	CO ₂ Me
335	H	PhCH ₂	Fmoc	H	H	CONHMe
336	H	PhCH ₂	Boc	H	H	CO ₂ Me
337	H	PhCH ₂	Boc	H	H	CONHMe
338	H	H	H	H	PhCH ₂	CO ₂ Me
339	H	H	H	H	PhCH ₂	CONHMe
340	H	H	PhCH ₂	H	PhCH ₂	CO ₂ Me
341	H	H	PhCH ₂	H	PhCH ₂	CONHMe
342	H	H	Fmoc	H	PhCH ₂	CO ₂ Me
343	H	H	Fmoc	H	PhCH ₂	CONHMe
344	H	H	Boc	H	PhCH ₂	CO ₂ Me
345	H	H	Boc	H	PhCH ₂	CONHMe

346	H	PhCH ₂	H	H	PhCH ₂	CO ₂ Me
347	H	PhCH ₂	H	H	PhCH ₂	CONHMe
348	H	PhCH ₂	PhCH ₂	H	PhCH ₂	CO ₂ Me
349	H	PhCH ₂	PhCH ₂	H	PhCH ₂	CONHMe
350	H	PhCH ₂	Fmoc	H	PhCH ₂	CO ₂ Me
351	H	PhCH ₂	Fmoc	H	PhCH ₂	CONHMe
352	H	PhCH ₂	Boc	H	PhCH ₂	CO ₂ Me
353	H	PhCH ₂	Boc	H	PhCH ₂	CONHMe
354	Ph	H	H	H	H	CO ₂ Me
355	Ph	H	H	H	H	CONHMe
356	Ph	H	PhCH ₂	H	H	CO ₂ Me
357	Ph	H	PhCH ₂	H	H	CONHMe
358	Ph	H	Fmoc	H	H	CO ₂ Me
359	Ph	H	Fmoc	H	H	CONHMe
360	Ph	H	Boc	H	H	CO ₂ Me
361	Ph	H	Boc	H	H	CONHMe
362	H	H	H	Ph	H	CO ₂ Me
363	H	H	H	Ph	H	CONHMe
364	H	H	PhCH ₂	Ph	H	CO ₂ Me
365	H	H	PhCH ₂	Ph	H	CONHMe
366	H	H	Fmoc	Ph	H	CO ₂ Me
367	H	H	Fmoc	Ph	H	CONHMe
368	H	H	Boc	Ph	H	CO ₂ Me
369	H	H	Boc	Ph	H	CONHMe
370	Ph	H	H	Ph	H	CO ₂ Me
371	Ph	H	H	Ph	H	CONHMe
372	Ph	H	PhCH ₂	Ph	H	CO ₂ Me
373	Ph	H	PhCH ₂	Ph	H	CONHMe
374	Ph	H	Fmoc	Ph	H	CO ₂ Me
375	Ph	H	Fmoc	Ph	H	CONHMe
376	Ph	H	Boc	Ph	H	CO ₂ Me

377	Ph	H	Boc	Ph	H	CONHMe
378	H	H	H	H	CH ₂ OH	CO ₂ Me
379	H	H	H	H	CH ₂ OH	CONHMe
380	H	H	PhCH ₂	H	CH ₂ OH	CO ₂ Me
381	H	H	PhCH ₂	H	CH ₂ OH	CONHMe
382	H	H	Fmoc	H	CH ₂ OH	CO ₂ Me
383	H	H	Fmoc	H	CH ₂ OH	CONHMe
384	H	H	Boc	H	CH ₂ OH	CO ₂ Me
385	H	H	Boc	H	CH ₂ OH	CONHMe
386	H	PhCH ₂	H	H	CH ₂ OH	CO ₂ Me
387	H	PhCH ₂	H	H	CH ₂ OH	CONHMe
388	H	PhCH ₂	PhCH ₂	H	CH ₂ OH	CO ₂ Me
389	H	PhCH ₂	PhCH ₂	H	CH ₂ OH	CONHMe
390	H	PhCH ₂	Fmoc	H	CH ₂ OH	CO ₂ Me
391	H	PhCH ₂	Fmoc	H	CH ₂ OH	CONHMe
392	H	PhCH ₂	Boc	H	CH ₂ OH	CO ₂ Me
393	H	PhCH ₂	Boc	H	CH ₂ OH	CONHMe
394	Ph	H	H	H	CH ₂ OH	CO ₂ Me
395	Ph	H	H	H	CH ₂ OH	CONHMe
396	Ph	H	PhCH ₂	H	CH ₂ OH	CO ₂ Me
397	Ph	H	PhCH ₂	H	CH ₂ OH	CONHMe
398	Ph	H	Fmoc	H	CH ₂ OH	CO ₂ Me
399	Ph	H	Fmoc	H	CH ₂ OH	CONHMe
400	Ph	H	Boc	H	CH ₂ OH	CO ₂ Me
401	Ph	H	Boc	H	CH ₂ OH	CONHMe

Table 4



Compound	R ₁	R ₂	R ₃	R' ₁	R' ₂	R ₃	X	Q'
402	H	H	H	H	H	H	O	CO-NH(CH ₂) ₂ NH-CO
403	H	H	H	H	H	H	O	CO-NH(CH ₂) ₄ NH-CO
404	H	H	H	H	H	H	O	CO-NH(CH ₂) ₆ NH-CO
405	H	H	H	H	H	H	O	CO-N(C ₂ H ₄)N-CO
406	H	H	PhCH ₂	H	H	PhCH ₂	O	CO-NH(CH ₂) ₂ NH-CO
407	H	H	PhCH ₂	H	H	PhCH ₂	O	CO-NH(CH ₂) ₄ NH-CO
408	H	H	PhCH ₂	H	H	PhCH ₂	O	CO-NH(CH ₂) ₆ NH-CO
409	H	H	PhCH ₂	H	H	PhCH ₂	O	CO-N(C ₂ H ₄)N-CO
410	H	H	PhCH ₂	H	H	PhCH ₂	H	CO-NH(CH ₂) ₂ NH-CO
411	H	H	PhCH ₂	H	H	PhCH ₂	H	CO-NH(CH ₂) ₄ NH-CO
412	H	H	PhCH ₂	H	H	PhCH ₂	H	CO-NH(CH ₂) ₆ NH-CO
413	H	H	PhCH ₂	H	H	PhCH ₂	H	CO-N(C ₂ H ₄)N-CO
414	H	PhCH ₂	PhCH ₂	H	PhCH ₂	PhCH ₂	O	CO-NH(CH ₂) ₂ NH-CO
415	H	PhCH ₂	PhCH ₂	H	PhCH ₂	PhCH ₂	O	CO-NH(CH ₂) ₄ NH-CO
416	H	PhCH ₂	PhCH ₂	H	PhCH ₂	PhCH ₂	O	CO-NH(CH ₂) ₆ NH-CO
417	H	PhCH ₂	PhCH ₂	H	PhCH ₂	PhCH ₂	O	CO-N(C ₂ H ₄)N-CO
418	H	PhCH ₂	PhCH ₂	H	PhCH ₂	PhCH ₂	H	CO-NH(CH ₂) ₂ NH-CO
419	H	PhCH ₂	PhCH ₂	H	PhCH ₂	PhCH ₂	H	CO-NH(CH ₂) ₄ NH-CO
420	H	PhCH ₂	PhCH ₂	H	PhCH ₂	PhCH ₂	H	CO-NH(CH ₂) ₆ NH-CO
421	H	PhCH ₂	PhCH ₂	H	PhCH ₂	PhCH ₂	H	CO-N(C ₂ H ₄)N-CO
422	Ph	H	PhCH ₂	Ph	H	PhCH ₂	O	CO-NH(CH ₂) ₂ NH-CO
423	Ph	H	PhCH ₂	Ph	H	PhCH ₂	O	CO-NH(CH ₂) ₄ NH-CO
424	Ph	H	PhCH ₂	Ph	H	PhCH ₂	O	CO-NH(CH ₂) ₆ NH-CO
425	Ph	H	PhCH ₂	Ph	H	PhCH ₂	O	CO-N(C ₂ H ₄)N-CO
426	Ph	H	PhCH ₂	Ph	H	PhCH ₂	H	CO-NH(CH ₂) ₂ NH-CO

427	Ph	H	PhCH ₂	Ph	H	PhCH ₂	H	CO-NH(CH ₂) ₄ NH-CO
428	Ph	H	PhCH ₂	Ph	H	PhCH ₂	H	CO-NH(CH ₂) ₆ NH-CO
429	Ph	H	PhCH ₂	Ph	H	PhCH ₂	H	CO-N(C ₂ H ₄)N-CO
430	Ph	H	PhCH ₂	Ph	H	PhCH ₂	H	CO-NH(CH ₂) ₂ NH-CO
431	Ph	H	PhCH ₂	Ph	H	PhCH ₂	H	CO-NH(CH ₂) ₄ NH-CO
432	Ph	H	PhCH ₂	Ph	H	PhCH ₂	H	CO-NH(CH ₂) ₆ NH-CO
433	Ph	H	PhCH ₂	Ph	H	PhCH ₂	H	CO-N(C ₂ H ₄)N-CO
434	Ph	H	Ph	Ph	H	Ph	O	CO-NH(CH ₂) ₂ NH-CO
435	Ph	H	Ph	Ph	H	Ph	O	CO-NH(CH ₂) ₄ NH-CO
436	Ph	H	Ph	Ph	H	Ph	O	CO-NH(CH ₂) ₆ NH-CO
437	Ph	H	Ph	Ph	H	Ph	O	CO-N(C ₂ H ₄)N-CO
438	NO ₂ -Ph	H	Ph	NO ₂ -Ph	H	Ph	O	CO-NH(CH ₂) ₂ NH-CO
439	NO ₂ -Ph	H	Ph	NO ₂ -Ph	H	Ph	O	CO-NH(CH ₂) ₃ NH-CO
440	NO ₂ -Ph	H	Ph	NO ₂ -Ph	H	Ph	O	CO-NH(CH ₂) ₄ NH-CO
441	NO ₂ -Ph	H	Ph	NO ₂ -Ph	H	Ph	O	CO-NH(CH ₂) ₅ NH-CO
442	NO ₂ -Ph	H	Ph	NO ₂ -Ph	H	Ph	O	CO-NH(CH ₂) ₆ NH-CO
443	NO ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	O	CO-N(C ₂ H ₄)N-CO
444	NH ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	O	CO-NH(CH ₂) ₂ NH-CO
445	NH ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	O	CO-NH(CH ₂) ₃ NH-CO
446	NH ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	O	CO-NH(CH ₂) ₄ NH-CO
447	NH ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	O	CO-NH(CH ₂) ₅ NH-CO
448	NH ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	O	CO-NH(CH ₂) ₆ NH-CO
449	NH ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	O	CO-N(C ₂ H ₄)N-CO
450	NO ₂ -Ph	H	Ph	NO ₂ -Ph	H	Ph	H	CO-NH(CH ₂) ₂ NH-CO
451	NO ₂ -Ph	H	Ph	NO ₂ -Ph	H	Ph	H	CO-NH(CH ₂) ₃ NH-CO
452	NO ₂ -Ph	H	Ph	NO ₂ -Ph	H	Ph	H	CO-NH(CH ₂) ₄ NH-CO
453	NO ₂ -Ph	H	Ph	NO ₂ -Ph	H	Ph	H	CO-NH(CH ₂) ₅ NH-CO
454	NO ₂ -Ph	H	Ph	NO ₂ -Ph	H	Ph	H	CO-NH(CH ₂) ₆ NH-CO
455	NO ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	H	CO-N(C ₂ H ₄)N-CO
456	NH ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	H	CO-NH(CH ₂) ₂ NH-CO
457	NH ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	H	CO-NH(CH ₂) ₃ NH-CO

458	NH ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	H	CO-NH(CH ₂) ₄ NH-CO
459	NH ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	H	CO-NH(CH ₂) ₅ NH-CO
460	NH ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	H	CO-NH(CH ₂) ₆ NH-CO
461	NH ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	H	CO-N(C ₂ H ₄)N-CO

In particular, as far as the dimers of formula (II) and (III) are concerned, all the possible combinations of the stereoisomers are possible, although not exactly specified in the above Table 3 and 4.

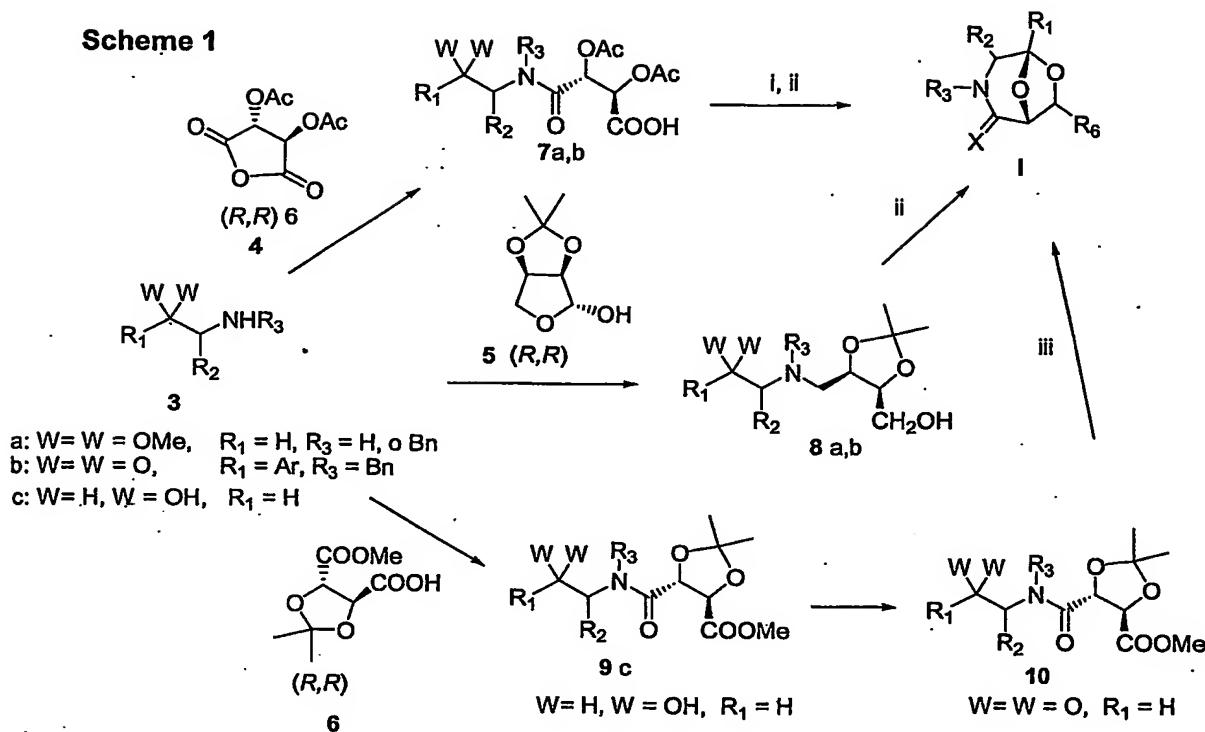
5 Furthermore, the present invention refers to the derivatives of 3-aza-bicyclo[3.2.1]octanes and their dimers that were prepared by the Applicants and described here for the first time, i.e. the 3-aza-bicyclo[3.2.1]octane derivatives (I) and their dimers of general formula (II) and (III) defined as above with exclusion of the following compounds: 1,2,5,7,8,9,10,12,13,17,19,20,21,32,34,35,36,38,40,44,

10 58,60,64,65,66,70,75,76,77,78,7983,87,91,95,99,101,103,138,145,152,154,163,1
64,168,172,174,176,178,184,186,192,322,324.

The compounds above cited are indeed already described in *J. Org. Chem.* 1999, 64, 7347; *Organic Letters*, 2000, 2, 3987-3990, *Bioorganic & Med Chem* 2001, 9, 1625,-1632, *Eur. J. Org. Chem.* 2002, 873-880, and in the European Application Patent No. 00104135.9-2117 and in the International Application No. WO 01/64686; in such documents the preparation methods of the compounds are also described.

20 The novel derivatives of 3-aza-bicyclo[3.2.1]octanes of general formula (I) and their dimers of general formula (II) and (III) may be prepared with the following process. The new compounds of general formula (I) and their correspondent dimers of formula (II) and (III), described for the first time in the present application may be prepared according the procedure described as following and represented in the following Scheme 1:

Scheme 1



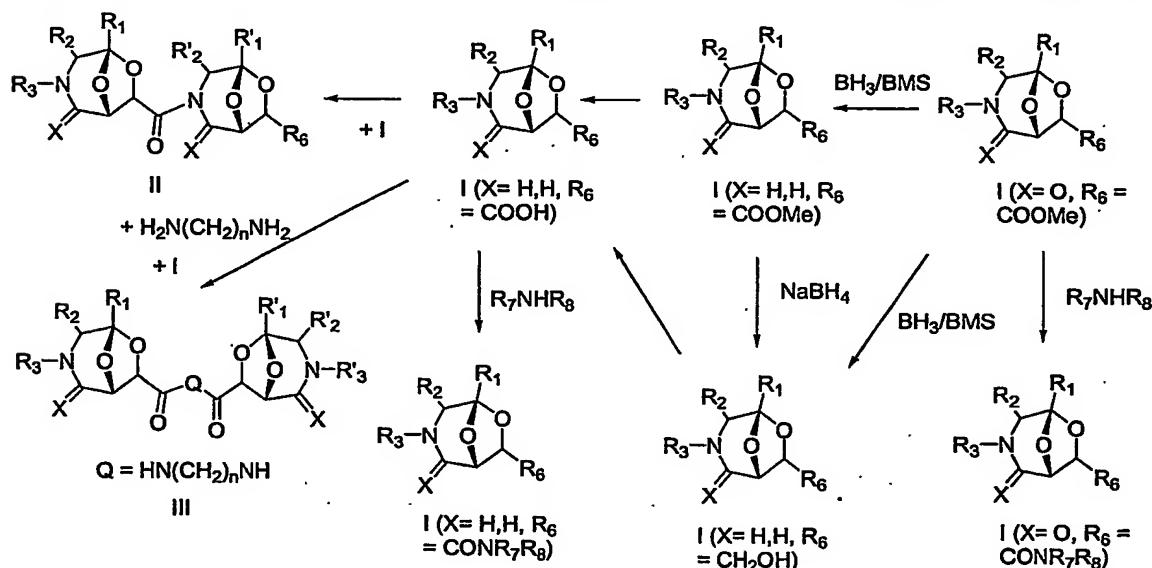
Protected alpha amino aldehydes (3a) or alpha amino ketones (3b) or alpha amino alcohols (3c) were reacted with - activated derivatives of tartaric acid as for example diacetylxytartaric anydride 4 (R,R o S,S), - or with acid tartaric

5 derivatives as for example the protected mono-methylester 6 (R,R or S,S), in the presence of coupling and activating agents - or by reductive amination with protected derivatives of erthrolactole 5 (R, R prepared from D-arabinose or S,S prepared from L-arabinose). The correspondent amides 7 e 9 (in the scheme 1 are shown only the R, R enantiomers, but the enantiomers S,S were prepared 10 analogously) or amine 8 (in the scheme 1 are shown only the R,S enantiomers, but the S,R enantiomers were prepared analogously). In the case of amide alcohol 9 the correspondent aldehyde or ketone 10 are obtained by oxidation. When R₃ is H in the amine 8, a Fmoc protection can be made. The further cyclisation of 15 compounds 7, 8 e 10 (Scheme 1) occurs by treatment with SOCl₂ and MeOH (reaction condition i) followed by treatment with sulfuric acid adsorbed on SiO₂ in refluxing toluene (reaction conditions ii) or by treatment with trifluoro acetic acid (TFA) pure or in methylene chloride (reaction conditions iii). Thus, starting from amides 7 and 10, the compounds I wherein X = O and R₆ = -COOMe in

configuration exo were prepared. In the case of amine 8 compounds I, wherein X = H, H and the group R₆ = -CH₂OH in endo configuration were prepared. The configuration R,R or S,S of stereocenters at C-1 bridgehead and at C-7 (bearing the carboxylic or hydroxymethyl group) is depending from that of tartaric acid or 5 from starting erythrolactole. The compounds I may be modified according to Scheme 2.

SCHEME 2

The compounds of formula (I) (amide type), wherein X = O may be reduced, by



10 using the complex BH₃ dimethyl sulfide, either to correspondent amino esters I (X = H, H, R₆ = COOMe), or to correspondent amino alcohol I (X=H, H e R₆ = CH₂OH). Such compounds may be deprotected to nitrogen atom. The hydrolysis 15 of amino ester I (X = H, H, R₆ = COOMe) may be done either in acid or basic conditions, giving to the correspondent amino acid I (X = H, H, R₆ = COOH). The amino acid is also obtained by Jones oxidation or by using PDC in DMF, from amino alcohol I (X=H, H e R₆ = CH₂OH), also after the change of the benzyl group to Boc or Fmoc. By activation of the carboxylic group an amide bond with an 20 amino NHR₇R₈ or an amino acid is formed. Otherwise, the activated carboxylic group of the amino acid I, is reacted with another unit of I having the deprotected nitrogen, to give the dimers of general formula (II) present in Table 3.

Otherwise, two units of a compound of formula (I) in each form, is reacted with a spacer Q, to give the dimers of general formula (III). The example shown in the scheme 2 includes but is not limited to the reaction of a diamine (Q) with two units of an activated carboxylic acid to give dimers of formula (III) reported in Table 4 .

5 The present 3-aza-bicyclo[3.2.1]octane derivatives of general formula (I) and their dimers of general formula (II) and (III), in free form or in form of pharmaceutically acceptable salts, may be used for preparation of pharmaceutical compositions following usual methods of pharmaceutical preparation.

Such pharmaceutical compositions may be formulated in conventional way, and

10 may include one or more excipients and/or diluent pharmaceutically acceptable. Administration of such formulations is feasible through any conventional route, such as parenteral, in the form of solution or suspension, oral, ocular, nasal, topical, etc.

15 The formulation of the 3-aza-bicyclo[3.2.1]octane derivatives of formula (I) and of their dimers of formula (II) and (III) according to the invention include tablets, capsules, pills, pellets, solutions, dispersions, suspensions, liposomal formulations, microspheres, nanospheres, creams and ointments, emulsions and aerosols, that can also be prepared in a way that allows a controlled or retarded release of the active compound.

20 Such pharmaceutical compositions may comprise at least one among the present compounds of formula (I), (II) and (III), or mixtures thereof, as active principle, possibly even in combination with other active principle or co-adjuvant, selected according to the pathologic conditions.

25 The pharmaceutical compositions comprising the compounds of the invention are suitable for pharmaceutical treatment of pathologic conditions related to the activity of neurotrophins.

30 The present derivatives of 3-aza-bicyclo[3.2.1] octane derivatives of general formula (I) and their dimers of general formula (II) showed neurotrophin agonist activity, especially of NGF, as they have the property of interacting with the NGF receptor complex at defined affinity levels. The agonist compounds have the property of inducing the biological signal of neurotrophins. The neurotrophin

agonist compounds are suitable for, e.g., preparation of pharmaceutical compositions useful in the treatment of:

- i) neurodegenerative, inflammatory, toxic, traumatic, or vascular disorders of the central, peripheral, or autonomic nervous system (such as Alzheimer Disease (AD), Amyotrophic Lateral Sclerosis (ALS), Huntington disease, multiple sclerosis, epilepsy, Down syndrome, nervous deafness, Ménière's disease), neural damages secondary to hypoxia, ischaemia, burns, chemotherapy, toxic compounds of various origin (including alcohol), infections (such as polio or HIV virus), trauma (including surgical trauma) originating axotomy of motoneurons, sensorial, motor, or sensorimotor neuropathies, or autonomic dysfunctions secondary to diverse pathologies (such as diabetes, renal insufficiency, or other systemic diseases), genetic disorders (such as Charcot-Marie-Tooth disease, Refsum disease, abetalipoproteinemia, Tangier disease, Krabbe disease, metachromatic leukodystrophy, Fabry disease, Dejerine-Sottas disease), nervous pathologies of diverse origin (such as diffuse atrophy of cerebral cortex, Lewy body dementia, Pick's disease, mesolimbocortical dementia, neuronal ceroid lipofuscinosis, thalamic degeneration, cortico-striatal-spinal degeneration, cortico-basal ganglionic degeneration, cerebro-cerebellar degeneration, familial dementia with spastic paraparesis, polyglucosan bodies disease, Shy-Drager synfrome, 20 olivopontocerebellar atrophy, progressive supranuclear palsy, deforming muscular dystony, Hallervorden-Spatz disease, Meige's syndrome, familial shivering, Gilles de la Tourette syndrome, chorea-acanthocytosis syndrome, Friedreich's ataxia, Holmes' corticocerebellar familial atrophy, Gerstmann-Straussler-Scheinker disease, progressive spinal muscular atrophy, spastic paraplegia, peroneal 25 muscular atrophy, hypertrophic interstitial polyneuropathy, polyneuritic ataxic heredopathy), some ocular pathologies (such as optic nerve neuropathies, retinal degeneration, ophtalmoplegy, glaucoma), corneal diseases of diverse origin (such as neurotrophic ulcers, post-traumatic or post-infective corneal disorders), pathologies from reduced motility of the gastro-intestinal tract or from urinary 30 bladder atony (such as interstitial cystitis or diabetic cystitis), endocrine neoplastic pathologies (such as prolactinoma), clinical conditions in which stimulation of learning processes is advantageous (in particular, in dementias and in post-

traumatic conditions), besides all pathological conditions originating from apoptotic processes of neural cells;

ii) acquired immunodeficiency diseases due to reduced or absent bioavailability of NGF (such immunodeficiency of ageing);

5 iii) conditions in which stimulation of neoangiogenesis may be advantageous (such as myocardial infarction, stroke, cerebral aneurysms, gastro-duodenal ulcers, wound healing, peripheral vasculopathies);
iv) certain ocular pathologies (such as corneal pathologies of diverse origin and glaucoma).

10 The present 3-aza-bicyclo[3.2.1]octane derivatives of general formula (I), and their dimers of general formula (II) and (III) above reported, are also suitable for the preparation of culture and storage media useful for conservation of explanted corneas destined to transplantation.

Moreover, when labelled with suitable reagents (contrast agents, radioisotopes,

15 fluorescent agents, etc.), and possibly processed with any other procedure useful for medical imaging purposes, the present 3-aza-bicyclo[3.2.1]octane derivatives of general formula (I), and their dimers of general formula (II) and (III), may be used for the imaging analysis of tissues and organs containing neurotrophine receptors, either *in vitro* or *in vivo*. In particular such labelled compounds may be

20 used either for monitoring the use and efficacy of drugs or for the diagnosis of mammal diseases in which the neurotrophine receptors are involved.

In general, the present compounds having neurotrophin agonistic activity, in particular NGF agonistic activity, were proven adequate to substitute for neurotrophin and NGF biologic activity.

25 Furthermore, the present neurotrophin agonistic compounds can be used to promote *in vivo*, *in vitro*, or *ex vivo* growth and/or survival of neural cells, including, but not limited to: dopaminergic, cholinergic, sensorial neurons, striatal cells, cortical cells, cells of the corpus striatum, hippocampus, cerebellum, olfactory bulbs, peri-aqueductal cells, cells of the raphe nuclei, of the locus coeruleus, of the

30 dorsal root ganglia, sympathetic neurons, lower motoneurons, nervous stem cells, or cells anyhow deriving from the neural plaque.

The following examples are reported to give a non-limiting illustration of the

present invention.

EXAMPLE 1

Preparation of methyl 3-benzyl-2-oxo-(1S,5S,7R)-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-exo-carboxylate (compound of formula (I) where X = O, 5 R₁ = H, R₂ = Bn, R₆ = (R)-COOMe) (Compound 1)

A solution of *R,R* tartaric anhydride 4 (4 g) (prepared as reported by Lucas H.J., Baumgarten W., *J.Am.Chem.Soc.*, 1941, 63, 1654) in anhydrous dichloromethane (23 ml) and 3a (where X = X = OMe, R₁ = H, R₂ = H, R₃ = Bn,) (3 g) prepared as reported (Kermak, W. O.; Perkin, W. H.; Robinson, R. *J. Chem. Soc., Trans.*, 1922, 10 121, 1872) were reacted at r. t. for 15 h. After evaporation of the solvent 7a (7 g), is obtained as an oil. To the crude product 7a in CH₃OH (40 ml), thionyl chloride is added dropwise (0.8 ml) at 0 °C and then the mixture heated at 60 °C for 15 h. After evaporation of solvent, the crude product dissolved in toluene (8 ml) is quickly added to a refluxed suspension of (1.6 g) H₂SO₄/SiO₂ (H₂SO₄ 30% by weight) in toluene (12.5 ml). After 15 min, one third of the solvent is distilled off and the remaining hot mixture is filtered on a short pad of NaHCO₃. After evaporation of the solvent, the crude product was purified by chromatography giving the pure compound of the title (2.8 g).

¹H NMR (CDCl₃) δ 7.32-7.16 (m, 5H), 5.84 (d, J=2.0 Hz, 1H), 4.96 (s, 1H), 4.74 (s, 1H), 4.52 (s, 2H), 3.77 (s, 3H), 3.34 (dd, J₁=12.0 Hz, J₂=2.0 Hz, 2H), 3.08 (J=12.0 Hz, 1H). P.f. 82, [α]²⁵_D = - 49 (c 1.0, CHCl₃)

EXAMPLE 2

Preparation of methyl (1R,5R,7S)-3-benzyl-2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-exo-carboxylate (compound of formula (I) where X = O, R₁ = R₂ = H, R₃ = Bn, R₆ = (S)-COOMe) (Compound 191)

Following the same procedure of Example 1, starting from anhydride *S,S* tartaric 4, the compound of the title is obtained.

¹H NMR (CDCl₃) δ 7.40-7.10 (m, 5H), 5.85 (d, J=2.0 Hz, 1H), 4.97 (s, 1H), 4.74 (s, 1H), 4.52 (s, 2H), 3.79 (s, 3H), 3.34 (dd, J₁=12.0 Hz, J₂=2.0 Hz, 2H), 3.09 (J=12.0 Hz, 1H). P.f. 83, [α]²⁵_D = + 48 (c 1.0, CHCl₃)

EXAMPLE 3

Preparation of methyl (1S,5S,7R)-3-benzyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-exo-carboxylate (compound of formula (I) where X = R₁ = R₂ = H, R₃ = Bn, R₆ = (R)-COOMe) (compound 40)

A solution of BH₃·Me₂S (1 M, 2.5 ml,) was slowly added at 0°C to a solution in 5 anhydrous THF (65 ml) of compound of formula (I) where X = O, R₁ = H, R₂ = H, R₃ = Bn, R₆ = (R)-COOMe (compound 1) (2.8 g) prepared as described above in Example 1. The mixture was stirred for 18 h at r. t. and then ethanol (3 ml), NaOH solution (3M, 2 ml) and H₂O (150 ml) were added. After extraction with diethylether, the organic phase was separated and evaporated giving, after 10 chromatography, the pure compound of the title (2 g) as colorless oil.

¹H NMR (CDCl₃) δ 7.30-7.23 (m, 5H), 5.62 (s, 1H), 4.78 (s, 1H), 4.60 (s, 1H), 3.74 (s, 3H), 3.55 (pd, 2H), 2.84 (d, J=13 Hz, 1H), 2.76 (d, J=10 Hz, 1H), 2.50 (dd, J₁=10 Hz, J₂=2 Hz, 1H), 2.30 (d, J=11 Hz, 1H). [α]²⁵_D = - 60 (c 1.0, CHCl₃).

EXAMPLE 4

Preparation of methyl (1S,5S,7R)-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-exo-carboxylate (compound of formula(I) where X = R₁ = R₂ = R₃ = H, R₆ = (R)-COOMe) (Compound 34)

To a suspension of compound of formula (I) where X = R₁ = R₂ = H, R₃ = Bn, R₆ = (R)-COOMe (compound 40) (2 g) prepared as described above in Example 3 and 20 Pd/C 10 % (1.3 g) in methanol (40 ml), is added ammonium formiate (2.4 g). The mixture left at reflux for 1h, was filtered on Celite and washed with CH₃OH. The solution is evaporated to give the compound of the title (1.3 g), as colorless oil. ¹H NMR (CDCl₃) δ 5.53 (s, 1H), 4.72 (s, 1H), 4.49 (s, 1H), 3.71 (s, 3H), 3.17 (dd, J₁=13.6 Hz, J₂=1.8 Hz, 1H), 2.83 (m, 2H), 2.68 (d, J=13.6 Hz, 1H), 2.55 (br, 1H). 25 [α]²⁵_D = - 55 (c 0.7, CHCl₃).

EXAMPLE 5

Preparation of acid (1S,5S,7R)-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-exo-carboxylic (compound of formula (I) where X = R₁ = R₂ = R₃ = H, R₆ = (R)-COOH) (Compound 32)

30 The compound of formula (I) where X = R₁ = R₂ = R₃ = H, R₆ = (R)-COOMe (Compound 34) prepared as described in Example 4 (0.5 g) was dissolved in a

solution of HCl (4N, 12 ml). After 18 h at r. t., the solution was evaporated obtaining the title compound as HCl salt (0.5 g).

$[\alpha]^{25}_D$ -38.3 (c 1.1, H₂O); ¹H NMR (D₂O) δ 5.95 (s, 1H), 5.06 (s, 1H), 5.04 (s, 1H), 3.58 (m, 2H), 3.34 (m, 2H);

5 EXAMPLE 6

Preparation of methyl (1S,5S,7R)-3-ter-butoxycarbonyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-exo-carboxylate (compound of formula (I) where X = R₁ = R₂ = H, R₃ = Boc, R₆ = (R)-COOMe) (Compound 42)

DIPEA (0.8 ml) and (BOC)₂O (1.1 g) were added to a solution in CH₂Cl₂ anhydrous (9 ml) and ethanol (3 ml) of the compound of formula (I) wherein X = R₁ = R₂ = R₃ = H, R₆ = (R)-COOMe (Compound 34) (0.8 g) prepared as described in Example 4. The reaction mixture was left for 18 h at r. t., the solvent was evaporated and the residue was treated with a solution of NaHSO₃ (5 %) and extracted with diethylether. After evaporation of the solvent, the crude product was purified by chromatography to give the title compound (0.8 g) as white solid.

¹H NMR (CDCl₃) δ 5.64 and 5.58 (rotamers) (s, 1H), 4.65 and 4.60 (rotamers) (s, 1H), 4.51 (s, 1H), 3.72 (s, 3H), 4.00-3.60 (m, 2H), 3.20 (m, 1H), 2.92 (m, 1H), 1.43 (s, 9H).

EXAMPLE 7

Preparation of (1S,5S,7R)-3-ter-butoxycarbonyl-6,8-dioxa-7-exo-hydroxymethyl-3-azabicyclo[3.2.1]octane (compound of formula (I) where X = R₁ = R₂ = H, R₃ = Boc, R₆ = (R)-CH₂OH) (Compound 62)

To a solution in MeOH (15 ml) of the compound of formula (I) where X = R₁ = R₂ = H, R₃ = Boc, R₆ = (R)-COOMe (Compound 42) (0.8 g) prepared as described in Example 6, at 0 °C, NaBH₄ (0.6 g) was added in small portions. After 10 min at r. t., the mixture was evaporated, and the crude product was purified by chromatography to give the compound of the title (0.5 g) as a colourless oil. $[\alpha]^{25}_D$ -30 (c 1.0, MeOH).

¹H NMR (CDCl₃) δ 5.50 and 5.44 (rotamers) (s, 1H), 4.32 and 4.27 (rotamers) (s, 1H), 4.18 (m, 1H), 3.88-3.67 (m, 2H), 3.56 (d, J=5.5 Hz, 2H), 3.21 (m, 1H), 2.96 (m, 1H), 1.92 (b, 1H), 1.43 (s, 9H).

EXAMPLE 8

Preparation of (1S,5S,7R)-3-(9-Fluorenylmethoxycarbonyl)-7-endo-hydroxymethyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane (compound of formula (I) where X = R₁ = R₂ = H, R₃ = Fmoc, R₆ = (R)-CH₂OH) (compound 61)

To a solution of 2,3-O-isopropylidene-D-erithrose (R,R) 5 (1.8 g) in THF (prepared

5 from D-Arabinose, as reported by Thompson, D.K.; Hubert, C.N.; Wightman, R.H. *Tetrahedron* 1993, 49, 3827-3840) 2,2-diethoxyethylamine 3a (where W= W= OEt, R₁ = R₂ = R₃ =H) (1.7 ml) a 0 °C, NaBH(OAc)₃ (3.1 g) was added in small portions. After 18h a r. t., the mixture is diluted with a saturated solution of NaHCO₃ and extracted with ethyl acetate. The organic phase was evaporated giving an oil, 10 which was chromatographed to give the product 8a (where W= W= OEt, R₁=R₂=R₃=H) as yellowish oil (1.9 g).

[α]²⁰_D -8.4 (c 0.54, CHCl₃); ¹H NMR (CDCl₃) δ 4.83 (br, 2 H), 4.59 (t, J = 5.5 Hz, 1 H), 4.32 (m, 2 H), 3.75-3.45 (m, 6 H), 3.05-2.83 (m, 2 H), 2.79 (d, J = 5.5 Hz, 2 H), 1.44 (s, 3 H), 1.34 (s, 3 H), 1.21 (t, J = 7.0 Hz, 6 H).

15 To a solution of 8a (where W= W= OEt, R₁=R₂=R₃=H) (1.7 g) in acetone (40 ml) Fmoc-O-Su (2.1 g) and an aqueous solution of Na₂CO₃·H₂O (0.75 g in 40 ml) were added at 0°C. The mixture was left at r.t. for 18 h, and extracted with CH₂Cl₂, then the solvent was evaporated and the residue was chromatographed to give the product 8a (where W= W= OEt, R₁=R₂=H, R₃ =Fmoc) as yellowish oil (2.2 g).

20 [α]²⁰_D -34 (c 0.38, MeOH); ¹H NMR (CDCl₃) δ 7.73 (d, J = 7.3 Hz, 2 H), 7.56 (m, 2 H), 7.34 (m, 4 H), 4.63 (m, 2 H), 4.47-4.14 (m, 3 H), 4.19 (t, J = 4.9 Hz, 1 H), 3.74-3.02 (m, 10 H), 1.42-1.04 (m, 12 H);

Compound 8a (where W= W= OEt, R₁=R₂=H, R₃ =Fmoc) (1.9 g) dissolved in trifluoroacetic acid (8 ml) was left aside for 18 h a r. t. After evaporation of TFA, the 25 crude compound, dissolved in MeOH, was filtered on as short pad of NaHCO₃, then the solvent was evaporated and the residue was chromatographed to give the title product as a white solid (1 g).

M.p. 41-42 °C; [α]²⁰_D -32 (c 0.5, CHCl₃); ¹H NMR (CDCl₃) δ 7.77 (d, J = 7.0 Hz, 2 H), 7.57 (d, J = 7.0 Hz, 2 H), 7.38 (m, 4 H), 5.51 (s, 1 H), 4.92-2.95 (m, 12 H).

30 EXAMPLE 9

Preparation of acid (1S,5S,7S)-3-(9-Fluorenylmethoxycarbonyl)-6,8-dioxa-3-aza-bicyclo[3.2.1]octan-7-endo carboxylic (compound of formula(I) where X = R₁ = R₂ = H, R₃ = Fmoc, R₆ = (S)-COOH) (Compound 39)

To a solution of the compound of formula (I) where X = R₁ = R₂ = H, R₃ = Fmoc, R₆

5 = (R)-CH₂OH (compound 61) (0.9 g) prepared according to the Example 8, in acetone (75 ml) was added the Jones reagent at 0°C, [prepared by slow addition of H₂SO₄ (2.8 ml) to a solution of CrO₃ (1.5 g) in H₂O (20 ml) a 0°C]. The mixture was left for 18 h at r.t and then was added with isopropanol, filtered on Celite and evaporated. The crude product dissolved in EtOAc (45 ml) was extracted with 10% 10 NaHCO₃ in water. After separation, the aqueous phase was acidified at pH 1 with HCl and extracted with EtOAc. Evaporation of the organic phase gave a crude product which was chromatographed to give the compound of the title (0.7 g) as a white solid.

M.p. 79-82°C; [α]²⁰_D -53 (c 0.5, CHCl₃), ¹H NMR (CDCl₃) δ 7.75 (m, 2H); 7.53 (d, 15 J = 7.0 Hz, 2H); 7.38 (m, 4H); 5.56 (s, 1H); 4.74-4.45 (m, 4H); 4.23-3.91 (m, 4H); 3.29-3.11 (m, 2H).

EXAMPLE 10

Preparation of (1R,5R,7R)-3-(9-Fluorenylmethoxycarbonyl)-6,8-dioxa-3-aza-bicyclo[3.2.1]octan-7-endo carboxylic acid (compound of formula (I) where X = R₁ = R₂ = H, R₃ = Fmoc, R₆ = (R)-COOH) (compound 218)

A solution of (1R,5R,7S)-3-(9-fluorenylmethoxycarbonyl)-7-endo-hydroxymethyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane (compound of formula (I) where X = R₁ = R₂ = H, R₃ = Fmoc, R₆ = (S)-CH₂OH) (1.8 g), prepared from (S,S) erythrose 5 (obtained starting from L-arabinose) with the same procedure above described in 25 the Example 8 for its enantiomer, was treated as above described in the Example 9 for its enantiomer, to give 1.4 g of the title compound as white solid.

M.p. 71-81 °C; [α]²⁰_D +52.9 (c 0.50, CHCl₃).

EXAMPLE 11

Preparation of methyl 3-benzyl-5-phenyl-2-oxo-(1S,5S,7R)-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-exo-carboxylate (compound of formula (I) where X = O, R₁ = Ph, R₂ = H, R₃ = Bn, R₆ = (R)-COOMe) (Compound 27)

To a solution of **3b** (2.4 g) (where X = O, R₁ = Ph, R₂ = H, R₃ = Bn,) (prepared according the procedure reported by R Simonoff and W.H Hartung, *J. Am. Pharm. Assoc.*, 35, 306, 1946) in dry CH₂Cl₂ (20 ml), (*R,R*) **6** acid tartaric derivative (2.49 g, 5.33 mmol) and DIPEA (5.4 ml) were added. The mixture was stirred at r. t. for 2 h, the solvent was evaporated to give an oil which was extracted in ethyl acetate. The solution was washed with solution of 5% KHSO₄, and 5% NaHCO₃ in water. After evaporation of the solvent the residue was purified by chromatography to give **8b** (where X = O, R₁ = Ph, R₂ = H, R₃ = Bn,) (3.2 g) as colourless oil.

¹H NMR δ 7.90-7.85 (m, 2 H), 7.61-7.22 (m, 8 H), 5.39 (d, J = 5.1 Hz, 1 H), 5.11 (d, J = 5.1 Hz, 1 H), 4.88-4.10 (m, 4 H), 3.80 (s, 3 H), 1.49 (s, 3 H), 1.31 (s, 3 H).

A solution of **8b** (3.2 g) (where X = O, R₁ = Ph, R₂ = H, R₃ = Bn,) in toluene (80 ml) was quickly added to a suspension of H₂SO₄/SiO₂ (30% w/w, 1.4 g) in toluene at reflux (120 ml). After 15 min one third of the solvent was distilled off and the hot remaining mixture was filtered on a short pad of NaHCO₃. After evaporation of the solvent the residue was purified by chromatography to give 2.4 g of the title compound as colorless solid.

M.p. 113-114 °C. [α]_D²⁵ -64.0 (c 1, CDCl₃). ¹H NMR δ 7.62-7.59 (m, 2 H), 7.41-7.24 (m, 8 H), 5.16 (s, 1 H), 4.92 (s, 1 H), 4.61 (m, 2 H), 3.74 (s, 3 H), 3.46 (m, 2 H).

EXAMPLE 12

Preparation of methyl 3-benzyl-5-phenyl-(1S,5S,7R)-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-exo-carboxylate (compound of formula (I) where X = R₂ = H, R₁ = Ph, R₃ = Bn, R₆ = (*R*)-COOMe) (Compound 120)

To a solution in dry THF (25 ml) of the compound of formula (I) where X = O, R₁ = Ph, R₂ = H, R₃ = Bn, R₆ = (*R*)-COOMe) (compound 27) prepared as described in Example 11 (2.5 mmol), at 0°C, BH₃Me₂S (10 M 0.5 ml, 4.9 mmol) was added dropwise. The mixture was left aside for 16 hr and then EtOH (1 ml), 3 M NaOH (1 ml) and H₂O (20 ml) were added. After extraction with diethylether, and evaporation of the solvent the residue was purified by chromatography to give 1 g of the compound of the title as colorless solid.

M.p. 97 °C. [α]_D²⁵ =13.0 (c 1, CHCl₃). ¹H NMR δ 7.72-7.58 (m, 2 H), 7.52-7.19 (m, 8 H), 5.00 (s, 1 H), 4.86 (s, 1 H), 3.75 (m 2 H), 3.78 (s, 3 H), 3.62 (m, 2 H), 3.16 (d, J= 11.2, 4 H), 2.93 (d, J= 11.6, 2 H), 2.63 (d, J= 11.0, 2 H).

EXAMPLE 13

Preparation of methyl (1S,4S,7R)-3,4-Dibenzyl-2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-exo-carboxylate (compound of formula (I) where X = O, R₁ = H, R₂ = (S)Bn, R₃ = Bn, R₆ = (R)-COOMe) (Compound 12)

5 To a solution of L-phenylalaninol **3c** (where W=H, W=OH, R₁ =H, R₂ = Bn, R₃ = H) (5 g) in MeOH (150 ml) benzaldehyde (3.3 ml) were added. The reaction mixture was stirred at r. t. for 1 h, then 1.2 g of NaBH₄, were added in small portions in 2 hr at 0°C. The solvent was evaporated and the residue extracted with 50 ml of HCl at pH=2. The aqueous solution was extracted with Et₂O, treated with Na₂CO₃ until pH=9 and then extracted with CHCl₃. The organic phase evaporated gave *N*-benzyl-(L)-phenylalaninol as white solid (7 g) **3c** (where W=H, W=OH, R₁ =H; R₂ = Bn, R₃ = Bn)

10

¹H NMR (CDCl₃) δ, ppm: 7.34-7.06 (m, 10 H), 3.73 (s, 2 H), 3.31 (dd, J = 6.2, 12.5 Hz, 1 H), 3.00-2.81 (m, 1H), 2.80-2.66 (m, 2 H). 2.62 (dd, J = 6.2, 12.5 Hz, 1 H)

15 To a solution of *N*-benzyl-(L)-phenylalaninol **3c** (2.8 g) in 23 ml of CHCl₃ at 0°C , DIPEA (4 ml), HOBr (2.1 ml) and a solution of methyl ester of (2R, 3R)-2,3-O-isopropylidene tartaric acid (**6**) (2.4 g) in 23 ml of CHCl₃, were added. Then 1.7 g of DIPC were added. After 72 hr at r. t., the solvent was evaporated and the crude product residue was purified by chromatography to give a yellowish solid (2.4 g)

20 **9c** (where W=H, W=OH, R₁ =H, R₂ = Bn, R₃ = Bn).

[α]_D²⁵ - 72 (c=0,5 , CHCl₃). ¹H NMR (CDCl₃), δ, ppm: (mixture of rotamers 2:1) major δ 7,40-7,05 (m, 10 H), 5,28 (d, J = 6,0 Hz, 1 H), 4,81 (d, J = 6,0 Hz, 1 H), 4,75 (d, J = 16,4 Hz, 1 H), 4,0 (d, J = 16,4 Hz, 1 H), 3,79 (s, 3 H), 3,70 (m, 1 H), 3,60 (m, 1 H), 3,46 (m, 1 H), 3,04 (m, 1 H), 1,52 (s, 3 H), 1,49 (s, 3 H).

25 The compound **9c** (where W=H, W=OH, R₁ =H, R₂ = Bn, R₃ = Bn) was oxidized to **10** (where W=O, W=O, R₁ =H, R₂ = Bn, R₃ = Bn) by Swern oxidation. 4.5 g of alcohol (**9c**) in 20 ml of CH₂Cl₂ were oxidized as usual by treatment with oxalyl chloride, DMSO and DIPEA. After usual work-up compound (**10**) (5 g) was obtained as yellow solid.

30 ¹H NMR (CDCl₃) δ ppm: 9,44 (s, 1 H), 7,40-7,00 (m, 10 H), 5,33 (d, J = 6,2 Hz, 1 H), 4,92 (d, J = 6,2 Hz, 1 H), 4,89 (d, J = 18,7 Hz, 1 H), 3,79 (s, 3 H), 3,53 (dd, J =

9,8, 4,3 Hz, 1 H), 3,44 (d, J = 18,7 Hz, 1 H), 3,41 (dd, J = 13,9, 4,3 Hz, 1 H), 3,12 (dd, J = 13,9, 9,8 Hz, 1 H), 1,54 (s, 3 H), 1,45 (s, 3 H).

5 The product was added in toluene (15 ml), to a suspension of 2.5 g SiO_2 and H_2SO_4 in 30 ml of refluxing toluene; After 30 min, After 15 min one third of the solvent was distilled off and the hot remaining mixture was filtered on a short pad of NaHCO_3 . After evaporation of the solvent the residue was purified by chromatography to give 3.2 g of the title compound.

10 ^1H NMR (CDCl_3) δ ppm: 7,40-7,15 (m, 8 H), 7,03 (m, 2 H), 5,51 (s, 1 H), 5,33 (d, J = 15,0 Hz, 1 H), 4,97 (s, 1 H), 4,71 (s, 1 H), 4,03 (d, J = 15,0 Hz, 1 H), 3,75 (s, 3 H), 3,32 (dd, J = 10,7, 3,7 Hz, 3 H), 3,15 (dd, J = 13,5, 3,7 Hz, 1 H), 2,75 (dd, J = 13,5, 10,7 Hz, 1 H)

EXAMPLE 14

15 Preparation of (1S,4S,7R)-3,4-Dibenzyl-6,8-dioxa-7-exo-hydroxymethyl 3-azabicyclo[3.2.1]octane (compound of formula (I) where $X = R_1 = H$, $R_2 = (S)\text{Bn}$, $R_3 = \text{Bn}$, $R_6 = (R)\text{-CH}_2\text{OH}$) (Compound 184)

20 To a solution in 100 ml of anhydrous THF of the compound of formula (I) where $X = O$, $R_1 = H$, $R_2 = (S)\text{Bn}$, $R_3 = \text{Bn}$, $R_6 = (R)\text{-COOMe}$ (compound 12) (4 g), prepared as described in Example 13, a solution $\text{BH}_3\text{-SMe}_2$ (3 ml, 10 M) in THF was added. After 38 hr at r. t. the reaction mixture was treated with dry EtOH (6ml) and 10% of 25 NaOH (6 ml), then diluted with 50 ml of water and extracted with Et_2O . After evaporation of the solvent the residue was purified by chromatography to give 1.7 g of the title compound as yellowish solid. $[\alpha]_D^{25} -59$ ($c = 0,2$, CHCl_3)

25 ^1H NMR (CDCl_3) δ , ppm: 7,40-7,00 (m, 10 H), 5,11 (s, 1 H), 4,39 (t, J = 5,1 Hz, 1 H), 4,24 (s, 1H), 3,81 (d, J = 13,6 Hz, 1 H), 3,63 (d, J = 13,6 Hz, 1 H) 3,52 (m, 2 H), 3,00 (m, 1 H) 3,00-2,80 (m, 2 H), 2,94 (d, J = 11,6 Hz, 1 H), 2,45 (dd, J = 11,6, 1,8 Hz, 1 H)

EXAMPLE 15

30 Preparation of dimer of formula (II) where $R_1 = R_1' = H$, $R_2 = R_3 = R_2' = \text{Bn}$, $R_6 = (R)\text{-COOMe}$ (Compound 348)

0.1 ml of DIPEA were added to a solution in 0.3 ml of CH_2Cl_2 of the compound of formula (I) where $X = R_1 = H$, $R_2 = (S)\text{-Bn}$, $R_3 = \text{Bn}$, $R_6 = (R)\text{-COOH}$ (Compound 188) (0.1 g) obtained by hydrolysis of the corresponding methyl ester (Compound

172) according to the procedure in Example 5. Then, 0.2 g of PyBroP at 0°C and 0.05 g (0.209 mmol) of the compound of formula (I) where X = R₁ = R₃ = H, R₂ = (S)-Bn, R₆ = (R)-COOMe (Compound 178) were added. The mixture was stirred overnight, the solvent evaporated and the residue dissolved in 50 ml of AcOEt.

5 After evaporation of the solvent the residue was purified by chromatography to give 0.07 g of the title compound as white solid.

EXAMPLE 16

Preparation of dimer of formula (III) where X = O, R₁ = R_{1'} = p-NO₂Ph, R₂ = R_{2'} = H, R₃ = R_{3'} = Ph, Q' = (CONH(CH₂)₆CONH) (Compound 441)

10 20 mg of (1R, 5S, 7R)-5-(4-Nitro-phenyl)-3-phenyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane-7-carboxylic acid methyl ester of formula (I) (Compound 31) (0.054 mmol) were added to 125.5 mg (1.08 mmol, 20 eq) of 1,6-diamino-hexane and the mixture heated at 65°C overnight. The crude is purified by chromatography (CH₂Cl₂-MeOH, 20:1 + NEt₃ 1%), thus obtaining 8 mg (0.018 mmol, 34 %) of a yellow solid corresponding to (1R, 5S, 7R)-5-(4-nitro-phenyl)-3-phenyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane-7-(6-amino-hexyl)-amide, i.e. the compound of formula (I) where X = O, R₁ = p-NO₂Ph, R₂ = H, R₃ = Ph, R₆ = CONH(CH₂)₆NH₂ (Compound 189) (R_f = 0.32) and 4 mg (0.0051 mmol, 10 %) of an orange solid corresponding to the dimeric compound of formula (III) of the title (R_f = 0.67).

- Compound 189: ¹H NMR (CDCl₃, δ): 8.32 (d, 2 H, J = 8.4 Hz), 7.83 (d, 2 H, J = 8.8 Hz), 7.30-7.22 (m, 2 H), 6.90-6.79 (m, 3 H), 6.25 (m, 1 H), 5.05 (s, 1 H), 4.74 (s, 1 H), 3.81-3.70 (m, 2 H), 3.28 (d, 1 H, J = 9.8 Hz), 3.20-3.10 (m, 2 H), 2.92 (d, 1 H, J = 11.6 Hz), 2.61 (m, 2 H), 1.78-1.15 (m, 10 H).

25 - dimeric compound of formula (III) of the title: ¹H NMR (CDCl₃, δ): 8.32 (d, 4 H, J = 8.8 Hz), 7.82 (d, 4 H, J = 10 Hz), 7.31-7.24 (m, 4 H), 6.91-6.80 (m, 6 H), 6.25 (m, 2 H), 5.05 (s, 2 H), 4.75 (s, 2 H), 3.81-3.71 (m, 4 H), 3.29 (d, 2 H, J = 11.6 Hz), 3.20-3.10 (m, 4 H), 2.92 (d, 2 H, J = 11.6 Hz), 1.54 (m, 4 H), 1.23 (m, 4 H).

BIOLOGICAL ACTIVITY

30 The biological activity of 3-aza-bicyclo(3.2.1)octanes of formula (I) and their dimeric forms of formula (II) and (III) was evaluated in different assays: induction of survival of PC12 cells in serum-free conditions, induction of proliferative activity

In PC3 prostatic carcinoma cell line, induction of VGF polypeptide synthesis, displacement of ^{125}I -NGF binding to specific surface receptor, and induction of Trk-A autophosphorylation. In all of these assays human recombinant (hr)NGF was used as internal standard.

5 Effect of compounds on PC12 cell survival in serum-free conditions.

The biological activity of 3-aza-bicyclo(3.2.1)octanes of formula (I) and their dimeric forms of formula (II) and (III) was tested as ability to induce the survival of PC12 cells in serum-free conditions by using hrNGF as internal standard.

PC12 cells were detached from tissue flasks with PBS-EDTA (physiological saline 10 solution added with ethylendiaminetetraacetic acid) and washed once with PBS to avoid residual amounts of serum. The cells were then diluted in RPMI-1640 medium without phenol red supplemented with penicillin and streptomycin and cultured in 96 well plates at the final concentration of 5×10^3 /well. Standard curve was performed by adding in triplicate cultures different concentrations of hrNGF, in 15 the range between 1-25 ng/ml. The compounds were instead added, in triplicate, at the final concentrations of 1, 10, 100 μM . The cells were then cultured for 60 hours at 37°C in a humidified, 5% CO₂, atmosphere. Then 10 μl of (3-[4,5-dimethylthiazol-2yl]-2,5-diphenyltetrazolium bromide (MTT, 0.5 mg/ml in isopropanol) were added to each well and plates, protected from the light, were left 20 at 37°C for 4 hours. At the end of incubation, 100 μl of 50% dimethylformamide (in 20% SDS; pH 7.4) were added to each well. Colorimetric reaction was detected with a 96 well plate reader by recording the absorbance at 570 nm. Results were expressed as survival induced by compounds/spontaneous survival $\times 100$.

Figure 1 shows the results obtained with 10 μM of the most representative 25 compounds and with 1 nM of hrNGF.

Effect of compounds on proliferative activity of PC3 cell line.

The ability of 3-aza-bicyclo(3.2.1)octanes of formula (I) and their dimeric forms of formula (II) and (III) with substitutions reported in Table 1-4 to induce proliferation of PC3 cell line, in serum-free conditions, was tested by using hrNGF as internal 30 standard.

PC3 cells were cultured in triplicate in 24 well plates at the final concentration of 10^4 cells/ml (final volume of 500 μl) in RPMI 1640 medium in the presence or

absence of 1, 10, 100 μ M of the compounds or of different concentration (between 1-25 ng/ml) of hrNGF as internal standard. Cells were incubated for 60 hours in humidified, 5% CO₂, atmosphere. At the end of incubation 0.5 μ Ci of ³H-thymidine were added to each well for 8 hours. Cells were then washed 6 times with PBS, 5 lysed with 0.1 % Triton-X100 in 0.1 M phosphate buffer, and the radioactivity was recorded in a β -scintillation counter. Results were expressed as ratio between ³H-thymidine incorporation (mean \pm SD) of stimulated cultures and ³H-thymidine incorporation of non stimulated cultures. Figure 2 shows the results obtained with 10 μ M of selected compounds or with 1 nM hrNGF as internal standard.

10 Induction of VGF production by PC12 cells

The ability of 3-aza-bicyclo(3.2.1)octanes of formula (I) and their dimeric forms of formula (II) and (III) with substitution reported in Table 1-4 was tested also as ability to induce VGF production by PC12 cells. 5 \times 10⁶ PC12 cells were cultured in the presence or absence of 1, 10, 100 μ M of the compounds or of 4 nM hrNGF as 15 internal standard for 24 hours in humidified, 5% CO₂, atmosphere. Cells were lysed in 0.25% NP-40 in PBS supplemented with 1 mM PMSF (phenyl-methyl) and 1 mM leupeptin and protein concentration was measured in each sample by Bradford assay. Equal amounts of proteins (30 μ g) were loaded in 8% SDS-polyacrilamide gel, electrophoresed, blotted onto nitrocellulose membrane and 20 stained with monoclonal antibodies anti-VGF followed by peroxidase-conjugated anti-mouse IgG. Reaction was visualized by Enhanced Chemiluminiscent Reagent (ECL, Amersham) following the manufacturer instruction.

Figure 3 shows the results obtained with 10 μ M of the selected (n. 91, 9, 323, 270) compounds or with 10 nM hrNGF. VGF is induced by the selected compounds as 25 well as by hrNGF.

Displacement of ¹²⁵I-NGF binding to PC12 cells

The ability of selected compounds to displace the binding of NGF to specific surface receptor was evaluated through the classic binding techniques of iodinated ligand.

30 PC12 cells were detached from tissue flasks with PBS-EDTA, washed with HKR medium (10 mM Hepes, 125 mM NaCl, 4.8 mM KCl, 1.3 mM CaCl₂, 1.2 mM MgSO₄, 1.2 mM KH₂PO₄, 1g/l glucose, 1g/l BSA) and incubated in triplicate in

HKR medium with 0.1 nM ^{125}I -NGF in the presence or absence of variable concentrations of the compounds to be assayed or of hrNGF as internal standard. Displacement curve was obtained by analyzing the resultant cell bound radioactivity in the presence of the compounds or of hrNGF with adequate software (Graphit 4).

Figure 4 a shows the displacement curve obtained with the compound n.9 used as competitor. The analysis of data revealed a K_d of $165 \text{ nM} \pm 0.05$. Figure 4b shows the displacement curve obtained by using hrNGF as competitor. The analysis of data revealed a K_d of $114 \text{ pM} \pm 0.01$ as already reported.

10 Trk-A autophosphorylation

To evaluate the ability of the compounds 3-aza-bicyclo(3.2.1)octanes of formula (I) and their dimeric forms of formula (II) and (III) reported in Table 1-4 to induce Trk-A autophosphorylation, PC12 cells were cultured in medium supplemented with 5% FBS for 48 hours, washed and equilibrated in serum-free medium for 2 hours. 15 2.5×10^6 cells were then stimulated with $10 \mu\text{M}$ of selected compounds for 30 min or with 10 nM hrNGF as positive control. Cells were then lysed with 0.5% Triton-X100 in PBS supplemented with protease inhibitors (PMSF, aprotinin, pepstatin, leupeptin) and phosphatase inhibitors. Protein concentrations in each sample was evaluated by Bradford assay and equal amounts (50 μg) of proteins were loaded 20 onto SDS-polyacrilamide gel, electrophoresed and blotted onto nitrocellulose membrane. Membranes was sained with rabbit anti-(Tyr 490 and Tyr 674/675) phosphorylated Trk-A (Cell Signaling Technology) used at the final dilution of 1:1000. After washing, membranes were stained with HRP-conjugated anti-rabbit IgG and the reaction was visualised by using ECL reagents following 25 manufacturing instructions.

Figure 5 shows the results obtained with the compounds 272, 325, 9, 91 and with hrNGF used as internal standard. The selected compounds are able to induce Trk-A autophosphorylation thus triggering the transduction of biological signals.

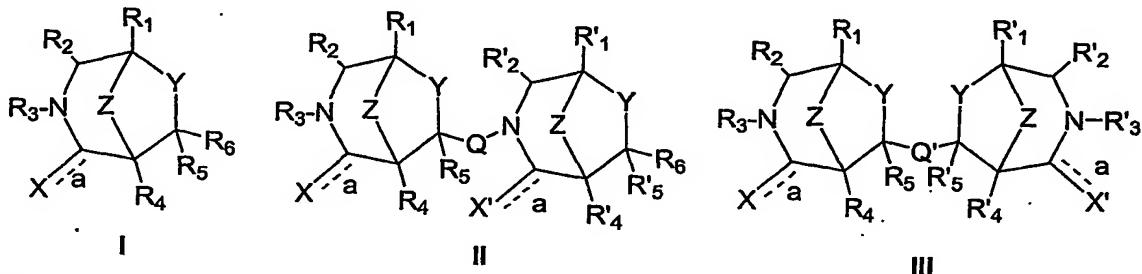
Synergic activity

30 The synergic activity of multiple combinations of 3-aza-bicyclo(3.2.1)octanes of formula (I) and their dimeric forms of formula (II) and (III) was evaluated in the PC12 survival assay in serum-free condition.

PC12 cells were seeded in 96 well plates at the concentration of 5×10^3 /well and cultured in triplicate in the presence or absence of $5 \mu\text{M}$ of selected compounds or of multiple combination of the same compounds at the final concentration of $10 \mu\text{M}$. 0.5 nM hrNGF was used as internal standard. After 60 hours at 37°C in a
5 humidified, 5% CO_2 , atmosphere, $10 \mu\text{l}$ of (3-[4,5-dimethylthiazol-2yl]-2,5-diphenyltetrazolium bromide (MTT, 0.5 mg/ml in isopropanol) were added to each well and plates, protected from the light, were left at 37°C for 4 hours. At the end of incubation, $100 \mu\text{l}$ of 50% dimethylformammide (in 20% SDS, pH 7,4) were
10 added to each well. Colorimetric reaction was detected with a 96 well plate reader by recording the absorbance at 570 nm. Results were expressed as survival induced by compounds/spontaneous survival *100. Figure 6 shows as selected combinations of 2 compounds (91 and 325) induce survival activity higher than the addition of activities induced by the single compound.

CLAIMS

1. A pharmaceutical composition comprising as active principle at least one among the 3-aza-bicyclo[3.2.1]octane derivatives of general formula (I); or their dimers of general formula (II) and (III), or mixtures thereof



5 wherein:

R₁ and R'₁, equal or different between each other, are selected from the group consisting of H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, heterocycle, arylC₁₋₈alkyl; heterocycleC₁₋₈alkyl, RR'N-C₁₋₈alkyl, RR'N-aryl, FmocNR'-aryl, BocNR'-aryl, CBzNR'-aryl; RO-aryl, R(O)C-aryl, RO(O)C-aryl, RR'N(O)C-aryl; FmocNR'-C₁₋₈alkyl, BocNR'-C₁₋₈alkyl, CbzNR'-C₁₋₈alkyl, FmocNR'-C₁₋₈aryl, BocNR'-C₁₋₈aryl and CbzNR'-C₁₋₈aryl,

10 R₂ and R'₂, equal or different between each other, are selected from the group consisting of H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, arylC₁₋₈alkyl, heterocycleC₁₋₈alkyl, aminoC₁₋₈alkyl, aminoaryl, C₁₋₈alkyloxyaryl, hydroxyaryl, 15 hydroxyC₁₋₈alkyl, carboxyC₁₋₈alkyl, methyloxycarbonylC₁₋₈alkyl, carboxyaryl, carboalkyloxyaryl, alkylcarbamoylaryl and -(side chains of amino acids), or

R₁ and R₂, taken together, and R'₁ and R'₂, taken together, are C₁₋₄alkyl, C₂₋₄ alkenyl, cycloalkyl or benzofused cycloalkyl, to form a bridge of 3, 4, 5, 6 terms,

20 R₃ and R'₃ are selected from the group consisting of H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cycloalkyl, aryl, arylC₁₋₈alkyl, heterocycleC₁₋₈alkyl, RR'NC₁₋₈alkyl, RR'N-aryl, RO-C₁₋₈alkyl, RO(O)C-C₁₋₈alkyl, R(O)C-C₁₋₈alkyl, RC(O)O-C₁₋₈alkyl, RC(O)N(R)C₁₋₈alkyl, RO-aryl, RO(O)C-aryl, R(O)C-aryl RC(O)O-aryl, RC(O)N(R)aryl, -CH(amino acid side-chain)CO₂R, -CH(amino acid side-chain)C(O)NR, -CH(CO₂R)- amino acid side-chain, CH(CONRR')- amino acid side-chain, Fmoc, Boc and Cbz,

25

R_4 , R'_4 R_5 , and R'_5 , equal or different amongst each other, are selected from the group consisting of H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkinyl, cycloalkyl, aryl, heterocycle, aryl C_{1-8} alkyl and heterocycle C_{1-8} alkyl,

R_6 is selected from the group consisting of H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, cycloalkyl, aryl, aryl C_{1-8} alkyl, heterocycle, heterocycle C_{1-8} alkyl; $-C(O)R$, $-C(O)OR$, $-C(O)NRR'$, CH_2OR , CH_2NRR' , $-C(O)NH-CH(\text{amino acid side-chain})C(O)OR$, $CH_2NR-Fmoc$, $CH_2NR-Boc$ and $CH_2NR-CBz$,

R and R' , equal or different between each other, are selected from the group consisting of H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, cycloalkyl, aryl, heterocycle, aryl C_{1-8} alkyl; heterocycle C_{1-8} alkyl; protecting group, $-C(O)CH(\text{amino acid side-chain})-NHT$, $-NH-CH(\text{amino acid side-chain})COOT$ and $-CH(\text{amino acid side-chain})COOT$,

where T is selected from between H and C_{1-8} alkyl;

X and X' , equal or different between each other, are selected from between O and S, when a is a double bond, or

X and X' are both H, when a is a single bond,

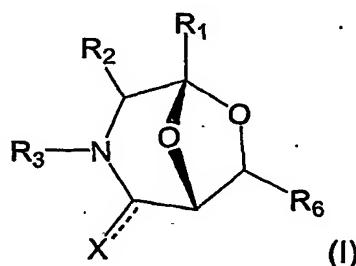
Y and Z , equal or different from each other, are selected from the group consisting of O, S, SO , SO_2 and $N-R$, wherein R is as above defined;

Q is selected from the group consisting of $C=O$, CH_2 , $CO-NH-CH(\text{amino acid side-chain})-CO$, $CONR(CH_2)_nCO$, $CONR-C_{2-8}$ alkenyl- CO $C(O)O(CH_2)_nCO$, $CH_2OC(O)(CH_2)_nCO$, and $CH_2NRC(O)(CH_2)_nCO$, wherein n is comprised between 2 and 6, and R is as above defined, Q is selected from the group consisting of $C(O)OCH_2$, $C(O)NRCH_2$, $CH_2OC(O)$, $CH_2NRC(O)$, $CONR(CH_2)_nNRCO$, $CONR-C_{2-8}$ alkenyl- $NRCO$, $C(O)O(CH_2)_nNRCO$, $CONR(CH_2)_nOC(O)$, $CH_2OC(O)(CH_2)_nOC(O)CH_2$, $CH_2OC(O)(CH_2)_nNRC(O)CH_2$, $CH_2NRC(O)(CH_2)_nOC(O)CH_2$, $CH_2NR(CH_2)_nNRCH_2$, $CH_2O(CH_2)_nOCH_2$, $CH_2O(CH_2)_nNRCH_2$, and $CH_2NR(CH_2)_nOCH_2$, wherein n is comprised between 2 and 6, and R is as above defined, and where the groups alkyl, alkenyl, alkynyl, cycloalkyl, aryl and the heterocyclic groups above reported, are possibly substituted.

2. The pharmaceutical composition according to claim 1, wherein in 3-aza-bicyclo[3.2.1]octane derivatives of formula (I) and in their dimers of formula (II) Z is O.

3. The pharmaceutical composition according to claim 1, wherein the alkyl, 5 alkenyl, alkynyl, cycloalkyl, aryl and heterocyclic groups may be substituted with one or more moieties chosen from the group consisting of halogen, cyano, nitro, amino, hydroxy, carboxylic acid, carbonyl and C₁₋₆ alkyl.

4. The pharmaceutical composition according to claim 1, wherein the 3-aza-bicyclo[3.2.1]octane derivatives of formula (I) and their dimers of formula (II) and 10 (III) are selected from the compounds having the following formulas:



Compound	X	R ₁	R ₂	R ₃	R ₆
1	O	H	H	PhCH ₂	(R) -CO ₂ Me
2	O	H	H	PhCH ₂	(S) -CO ₂ Me
3	O	H	H	PhCH ₂	(R)-CONCyclohexyl
4	O	H	H	PhCH ₂	(R)-CONCyclopentyl
5	O	H	(S) -Me	PhCH ₂	(R) -CO ₂ Me
6	O	H	(S) -Me	PhCH ₂	(S) -CO ₂ Me
7	O	H	(R) -Me	PhCH ₂	(R) -CO ₂ Me
8	O	H	(R) -Me	PhCH ₂	(S) -CO ₂ Me
9	O	H	(R) -CH ₂ Ph	PhCH ₂	(S) -CO ₂ Me
10	O	H	(R) -CH ₂ Ph	PhCH ₂	(R) -CO ₂ Me

11	O	H	(S)-CH ₂ Ph	PhCH ₂	(S)-CO ₂ Me
12	O	H	(S)-CH ₂ Ph	PhCH ₂	(R)-CO ₂ Me
13	O	H	(S)-CH ₂ OBn	PhCH ₂	(R)-CO ₂ Me
14	O	H	(S)-CH ₂ OBn	PhCH ₂	(S)-CO ₂ Me
15	O	H	(R)-CH ₂ OBn	PhCH ₂	(R)-CO ₂ Me
16	O	H	(R)-CH ₂ OBn	PhCH ₂	(S)-CO ₂ Me
17	O	H	(S)-CH ₂ OH	PhCH ₂	(R)-CO ₂ Me
18	O	H	(S)-CH ₂ OH	PhCH ₂	(S)-CO ₂ Me
19	O	H	(R)-CH ₂ OH	PhCH ₂	(R)-CO ₂ Me
20	O	H	(R)-CH ₂ OH	PhCH ₂	(S)-CO ₂ Me
21	O	H	=CH ₂	PhCH ₂	(R)-CO ₂ Me
22	O	H	=CH ₂	PhCH ₂	(S)-CO ₂ Me
23	O	H	(R)-CH ₂ OH	PhCH ₂	(S)-CO ₂ Me
24	S	H	H	PhCH ₂	(R)-CO ₂ Me
25	S	H	H	PhCH ₂	(R)-CONH(CH ₂) ₂ NH ₂
26	S	H	H	PhCH ₂	(R)-CONH(CH ₂) ₂ OH
27	O	Ph	H	PhCH ₂	(R)-CO ₂ Me
28	O	Ph	H	PhCH ₂	(S)-CO ₂ Me
29	O	Ph	H	CH(Ph) ₂	(R)-CO ₂ Me
30	O	Ph	H	CH(Ph) ₂	(S)-CO ₂ Me
31	O	NO ₂ -Ph	H	Ph	(S)-CO ₂ Me
32	H	H	H	H	(R)-CO ₂ H
33	H	H	H	H	(S)-CO ₂ H
34	H	H	H	H	(R)-CO ₂ Me
35	H	H	H	H	(S)-CO ₂ Me
36	H	H	H	PhCH ₂	(R)-CO ₂ H
37	H	H	H	PhCH ₂	(S)-CO ₂ H
38	H	H	H	Fmoc	(R)-CO ₂ H
39	H	H	H	Fmoc	(S)-CO ₂ H
40	H	H	H	PhCH ₂	(R)-CO ₂ Me

41	H	H	H	PhCH ₂	(S) -CO ₂ Me
42	H	H	H	Boc	(R) -CO ₂ Me
43	H	H	H	Boc	(S) -CO ₂ Me
44	H	H	H	Fmoc	(R) -CO ₂ Me
45	H	H	H	Fmoc	(S) -CO ₂ Me
46	H	H	H	H	(R) -CONHMe
47	H	H	H	H	(S) -CONHMe
48	H	H	H	Ac	(R) -CONHMe
49	H	H	H	Ac	(S) -CONHMe
50	H	H	H	PhCH ₂	(R) -CONHMe
51	H	H	H	PhCH ₂	(S) -CONHMe
52	H	H	H	Fmoc	(R) -CONHMe
53	H	H	H	Fmoc	(S) -CONHMe
54	H	H	H	PhCH ₂	(R)-CON 
55	H	H	H	PhCH ₂	(R) -CONH 
56	H	H	H	PhCH ₂	(R) -CON 
57	H	H	H	PhCH ₂	(R)-CONH(CH ₂) ₂ OH
58	H	H	H	H	(R) -CH ₂ OH
59	H	H	H	H	(S) -CH ₂ OH
60	H	H	H	Fmoc	(S) -CH ₂ OH
61	H	H	H	Fmoc	(R) -CH ₂ OH
62	H	H	H	Boc	(R) -CH ₂ OH
63	H	H	H	Boc	(S) -CH ₂ OH
64	H	H	H	PhCH ₂	(R) -CH ₂ OH
65	H	H	H	PhCH ₂	(S) -CH ₂ OH

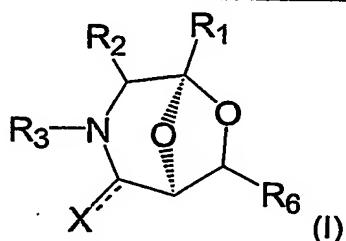
66	H	H	(S) -CH ₂ OBn	PhCH ₂	(R) -CO ₂ Me
67	H	H	(S) -CH ₂ OBn	PhCH ₂	(S) -CO ₂ Me
68	H	H	(R) -CH ₂ OBn	PhCH ₂	(R) -CO ₂ Me
69	H	H	(R) -CH ₂ OBn	PhCH ₂	(S) -CO ₂ Me
70	H	H	(S) -CH ₂ OBn	PhCH ₂	(R) -CH ₂ OH
71	H	H	(S) -CH ₂ OBn	PhCH ₂	(S) -CH ₂ OH
72	H	H	(R) -CH ₂ OBn	PhCH ₂	(R) -CH ₂ OH
73	H	H	(R) -CH ₂ OBn	PhCH ₂	(S) -CH ₂ OH
75	H	H	(S) -COOH	Fmoc	(R) -CO ₂ Me
76	H	H	(S) -COOH	Fmoc	(S) -CO ₂ Me
77	H	H	(R) -COOH	Fmoc	(R) -CO ₂ Me
78	H	H	(R) -COOH	Fmoc	(S) -CO ₂ Me
79	H	H	(S) -CH ₂ OBn	Fmoc	(R) -CO ₂ Me
80	H	H	(S) -CH ₂ OBn	Fmoc	(S) -CO ₂ Me
81	H	H	(R) -CH ₂ OBn	Fmoc	(R) -CO ₂ Me
82	H	H	(R) -CH ₂ OBn	Fmoc	(S) -CO ₂ Me
83	H	H	(S) -CH ₂ OBn	H	(R) -CO ₂ Me
84	H	H	(S) -CH ₂ OBn	H	(S) -CO ₂ Me
85	H	H	(R) -CH ₂ OBn	H	(R) -CO ₂ Me
86	H	H	(R) -CH ₂ OBn	H	(S) -CO ₂ Me
87	H	H	(S) -CH ₂ OH	H	(R) -CO ₂ Me
88	H	H	(S) -CH ₂ OH	H	(S) -CO ₂ Me
89	H	H	(R) -CH ₂ OH	H	(R) -CO ₂ Me
90	H	H	(R) -CH ₂ OH	H	(S) -CO ₂ Me
91	H	H	(S) -CH ₂ OH	Fmoc	(R) -CO ₂ Me
92	H	H	(S) -CH ₂ OH	Fmoc	(S) -CO ₂ Me
93	H	H	(R) -CH ₂ OH	Fmoc	(R) -CO ₂ Me
94	H	H	(R) -CH ₂ OH	Fmoc	(S) -CO ₂ Me
95	H	H	(S) -CH ₂ OH	Fmoc	(R) -CO ₂ Me
96	H	H	(S) -CH ₂ OH	Fmoc	(S) -CO ₂ Me
97	H	H	(R) -CH ₂ OH	Fmoc	(R) -CO ₂ Me

98	H	H	(R) -CH ₂ OH	Fmoc	(S) -CO ₂ Me
99	H	H	(S) -CH ₂ OH	PhCH ₂	(S) -CO ₂ Me
100	H	H	(R) -CH ₂ OH	PhCH ₂	(R) -CO ₂ Me
101	H	H	(R) -CH ₂ OH	PhCH ₂	(R) -CO ₂ Me
102	H	H	(R) -CH ₂ OH	PhCH ₂	(S) -CO ₂ Me
103	H	H	(S) -CH ₂ OH	Fmoc	(R) -CH ₂ OH
104	H	H	(S) -CH ₂ OH	Fmoc	(S) -CH ₂ OH
105	H	H	(R) -CH ₂ OH	Fmoc	(R) -CH ₂ OH
106	H	H	(R) -CH ₂ OH	Fmoc	(S) -CH ₂ OH
107	H	H	(S) -CH ₂ OH	PhCH ₂	(R) -CH ₂ OH
108	H	H	(S) -CH ₂ OH	PhCH ₂	(S) -CH ₂ OH
109	H	H	(R) -CH ₂ OH	PhCH ₂	(R) -CH ₂ OH
110	H	H	(R) -CH ₂ OH	PhCH ₂	(S) -CH ₂ OH
111	H	H	=CH ₂	PhCH ₂	(R) -CO ₂ Me
112	H	H	=CH ₂	PhCH ₂	(S) -CO ₂ Me
113	H	H	=CH ₂	PhCH ₂	(R) -CH ₂ OH
114	H	H	=CH ₂	PhCH ₂	(S) -CH ₂ OH
115	H	H	(S)-CH ₂ CH(Me) ₂	Fmoc	(R) -CH ₂ OH
116	H	H	(S)-CH ₂ CH(Me) ₂	PhCH ₂	(S) -CH ₂ OH
117	H	H	(S)-CH ₂ CH(Me) ₂	H	(R) -CH ₂ OH
118	H	Ph	H	H	(R) -CO ₂ Me
119	H	Ph	H	Fmoc	(R) -CO ₂ Me
120	H	Ph	H	PhCH ₂	(R) -CO ₂ Me
121	H	Ph	H	CH(Ph) ₂	(R) -CO ₂ Me
122	H	Ph	H	H	(S) -CO ₂ Me
123	H	Ph	H	Fmoc	(S) -CO ₂ Me
124	H	Ph	H	PhCH ₂	(S) -CO ₂ Me
125	H	Ph	H	CH(Ph) ₂	(S) -CO ₂ Me
126	H	p-NH ₂ -C ₆ H ₄	H	Ph	(S)-COOMe
127	H	p-NH ₂ -C ₆ H ₄	H	Ph	(S)-COOH
128	H	p-NH ₂ -C ₆ H ₄	H	Ph	(S)-CONHCH ₂ CO ₂ Me

129	H	p-NH-(Asp(O ^t Bu)-NH ₂)C ₆ H ₄	H	Ph	(S)-CO ₂ Me
130	H	p-NH-(Asp(O ^t Bu)NH ₂)-C ₆ H ₄	H	Ph	(S)-CO ₂ H
131	H	p-NH-(Asp(O ^t Bu)-NH ₂)C ₆ H ₄	H	Ph	(S)-CONH-Lys(NHBoc)-OMe
132	H	p-NH-(Asp(OH)-NH ₂)-C ₆ H ₄	H	Ph	(S)-CONH-Lys-OMe
133	H	p-NO ₂ -C ₆ H ₄	H	Ph	(S)-COOH
134	H	p-NO ₂ -C ₆ H ₄	H	Ph	(S)-COOMe
135	H	p-NO ₂ -C ₆ H ₄	H	Ph	(S)-CONHCH ₂ CO ₂ Me
136	H	Ph	H	H	(R)-CH ₂ OH
137	H	Ph	H	Fmoc	(R)-CH ₂ OH
138	H	Ph	H	PhCH ₂	(R)-CH ₂ OH
139	H	Ph	H	CH(Ph) ₂	(R)-CH ₂ OH
140	H	Ph	H	H	(S)-CH ₂ OH
141	H	Ph	H	Fmoc	(S)-CH ₂ OH
142	H	Ph	H	PhCH ₂	(S)-CH ₂ OH
143	H	Ph	H	CH(Ph) ₂	(S)-CH ₂ OH
144	H	H	(S)-Me	Fmoc	(R)-CO ₂ H
145	H	H	(S)-Me	Fmoc	(S)-CO ₂ H
146	H	H	(R)-Me	Fmoc	(R)-CO ₂ H
147	H	H	(R)-Me	Fmoc	(S)-CO ₂ H
148	H	H	(S)-Me	Fmoc	(R)-CO ₂ Me
149	H	H	(S)-Me	Fmoc	(S)-CO ₂ Me
150	H	H	(R)-Me	Fmoc	(R)-CO ₂ Me
151	H	H	(R)-Me	Fmoc	(S)-CO ₂ Me

152	H	H	(S) -Me	PhCH ₂	(R) -CO ₂ Me
153	H	H	(S) -Me	PhCH ₂	(S) -CO ₂ Me
154	H	H	(R) -Me	PhCH ₂	(R) -CO ₂ Me
155	H	H	(R) -Me	PhCH ₂	(S) -CO ₂ Me
156	H	H	(S) -Me	Fmoc	(R) -CH ₂ OH
157	H	H	(S) -Me	Fmoc	(S) -CH ₂ OH
158	H	H	(R) -Me	Fmoc	(R) -CH ₂ OH
159	H	H	(R) -Me	Fmoc	(S) -CH ₂ OH
160	H	H	(S) -Me	PhCH ₂	(R) -CH ₂ OH
161	H	H	(S) -Me	PhCH ₂	(S) -CH ₂ OH
162	H	H	(R) -Me	PhCH ₂	(R) -CH ₂ OH
163	H	H	(R) -Me	PhCH ₂	(S) -CH ₂ OH
164	H	H	(S) -PhCH ₂	Fmoc	(R) -CO ₂ H
165	H	H	(S) -PhCH ₂	Fmoc	(S) -CO ₂ H
166	H	H	(R) -PhCH ₂	Fmoc	(R) -CO ₂ H
167	H	H	(R) -PhCH ₂	Fmoc	(S) -CO ₂ H
168	H	H	(S) -PhCH ₂	Fmoc	(R) -CO ₂ Me
169	H	H	(S) -PhCH ₂	Fmoc	(S) -CO ₂ Me
170	H	H	(R) -PhCH ₂	Fmoc	(R) -CO ₂ Me
171	H	H	(R) -PhCH ₂	Fmoc	(S) -CO ₂ Me
172	H	H	(S) -PhCH ₂	PhCH ₂	(R) -CO ₂ Me
173	H	H	(S) -PhCH ₂	PhCH ₂	(S) -CO ₂ Me
174	H	H	(R) -PhCH ₂	PhCH ₂	(R) -CO ₂ Me
175	H	H	(R) -PhCH ₂	PhCH ₂	(S) -CO ₂ Me
176	H	H	(R) -PhCH ₂	H	(R) -CO ₂ Me
177	H	H	(R) -PhCH ₂	H	(S) -CO ₂ Me
178	H	H	(S) -PhCH ₂	H	(R) -CO ₂ Me
179	H	H	(S) -PhCH ₂	H	(S) -CO ₂ Me
180	H	H	(S) -PhCH ₂	Fmoc	(R) -CH ₂ OH
181	H	H	(S) -PhCH ₂	Fmoc	(S) -CH ₂ OH
182	H	H	(R) -PhCH ₂	Fmoc	(R) -CH ₂ OH

183	H	H	(R) -PhCH ₂	Fmoc	(S) -CH ₂ OH
184	H	H	(S) -PhCH ₂	PhCH ₂	(R) -CH ₂ OH
185	H	H	(S) -PhCH ₂	PhCH ₂	(S) -CH ₂ OH
186	H	H	(R) -PhCH ₂	PhCH ₂	(R) -CH ₂ OH
187	H	H	(R) -PhCH ₂	PhCH ₂	(S) -CH ₂ OH
188	H	H	(S)-PhCH ₂	PhCH ₂	(R)-COOH
189	O	p-NO ₂ Ph	H	Ph	CONH(CH ₂) ₆ NH ₂



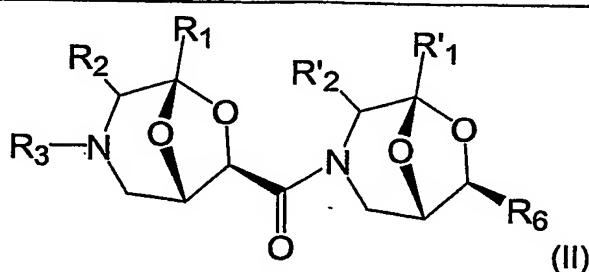
Compound	X	R ₁	R ₂	R ₃	R ₆
190	O	H	H	PhCH ₂	(R) -CO ₂ Me
191	O	H	H	PhCH ₂	(S) -CO ₂ Me
192	O	H	(S) -Me	PhCH ₂	(R) -CO ₂ Me
193	O	H	(S) -Me	PhCH ₂	(S) -CO ₂ Me
194	O	H	(R) -Me	PhCH ₂	(R) -CO ₂ Me
195	O	H	(R) -Me	PhCH ₂	(S) -CO ₂ Me
196	O	H	(S) -PhCH ₂	PhCH ₂	(R) -CO ₂ Me
197	O	H	(S) -PhCH ₂	PhCH ₂	(S) -CO ₂ Me
198	O	H	(R) -PhCH ₂	PhCH ₂	(R) -CO ₂ Me
199	O	H	(R) -PhCH ₂	PhCH ₂	(S) -CO ₂ Me
200	O	H	(S) -CH ₂ CH(Me) ₂	PhCH ₂	(R) -CO ₂ Me
201	O	H	(S) -CH ₂ CH(Me) ₂	PhCH ₂	(S) -CO ₂ Me
202	O	H	(R) -CH ₂ CH(Me) ₂	PhCH ₂	(R) -CO ₂ Me
203	O	H	(R) -CH ₂ CH(Me) ₂	PhCH ₂	(S) -CO ₂ Me
204	O	H	H	PhCH ₂	(R) -CONHMe
205	O	H	H	PhCH ₂	(S) -CONHMe
206	O	H	(S) -Me	PhCH ₂	(R) -CONHMe

207	O	H	(S)-Me	PhCH ₂	(S)-CONHMe
208	O	H	(R)-Me	PhCH ₂	(R)-CONHMe
209	O	H	(R)-Me	PhCH ₂	(S)-CONHMe
210	O	H	(S)-PhCH ₂	PhCH ₂	(R)-CONHMe
211	O	H	(S)-PhCH ₂	PhCH ₂	(S)-CONHMe
212	O	H	(R)-PhCH ₂	PhCH ₂	(R)-CONHMe
213	O	H	(R)-PhCH ₂	PhCH ₂	(S)-CONHMe
214	O	H	(S)-CH ₂ CH(Me) ₂	PhCH ₂	(R)-CONHMe
215	O	H	(S)-CH ₂ CH(Me) ₂	PhCH ₂	(S)-CONHMe
216	O	H	(R)-CH ₂ CH(Me) ₂	PhCH ₂	(R)-CONHMe
217	O	H	(R)-CH ₂ CH(Me) ₂	PhCH ₂	(S)-CONHMe
218	H	H	H	Fmoc	(R)-CO ₂ H
219	H	H	H	Fmoc	(R)-CO ₂ Me
220	H	H	H	Fmoc	(S)-CO ₂ H
221	H	H	H	Fmoc	(S)-CO ₂ Me
222	H	H	(S)-Me	Fmoc	(R)-CO ₂ H
223	H	H	(S)-Me	Fmoc	(R)-CO ₂ Me
224	H	H	(S)-Me	PhCH ₂	(R)-CO ₂ Me
225	H	H	(R)-Me	Fmoc	(R)-CO ₂ H
226	H	H	(R)-Me	Fmoc	(R)-CO ₂ Me
227	H	H	(R)-Me	PhCH ₂	(R)-CO ₂ Me
228	H	H	(S)-Me	Fmoc	(S)-CO ₂ H
229	H	H	(S)-Me	Fmoc	(S)-CO ₂ Me
230	H	H	(S)-Me	PhCH ₂	(S)-CO ₂ Me
231	H	H	(R)-Me	Fmoc	(S)-CO ₂ H
232	H	H	(R)-Me	Fmoc	(S)-CO ₂ Me
233	H	H	(R)-Me	PhCH ₂	(S)-CO ₂ Me
234	H	H	(S)-PhCH ₂	Fmoc	(R)-CO ₂ H
235	H	H	(S)-PhCH ₂	Fmoc	(R)-CO ₂ Me
236	H	H	(S)-PhCH ₂	PhCH ₂	(R)-CO ₂ Me
237	H	H	(R)-PhCH ₂	Fmoc	(R)-CO ₂ H

238	H	H	(R)- PhCH ₂	Fmoc	(R) -CO ₂ Me
239	H	H	(R)- PhCH ₂	PhCH ₂	(R) -CO ₂ Me
240	H	H	(S)- PhCH ₂	Fmoc	(S) -CO ₂ H
241	H	H	(S)- PhCH ₂	Fmoc	(S) -CO ₂ Me
242	H	H	(S)- PhCH ₂	PhCH ₂	(S) -CO ₂ Me
243	H	H	(R)- PhCH ₂	Fmoc	(S) -CO ₂ H
244	H	H	(R)- PhCH ₂	Fmoc	(S) -CO ₂ Me
245	H	H	(R)- PhCH ₂	PhCH ₂	(S) -CO ₂ Me
246	H	H	(R)- CH ₂ OH	Fmoc	(S) -CO ₂ Me
247	H	H	(R)- CH ₂ OH	PhCH ₂	(S) -CO ₂ Me
248	H	H	(R)- CH ₂ OBn	Fmoc	(S) -CO ₂ Me
249	H	H	(R)- CH ₂ OBn	PhCH ₂	(S) -CO ₂ Me
250	H	H	(R)- CH ₂ OH	Fmoc	(R) -CO ₂ Me
251	H	H	(R)- CH ₂ OH	PhCH ₂	(R) -CO ₂ Me
252	H	H	(R)- CH ₂ OBn	Fmoc	(R) -CO ₂ Me
253	H	H	(R)- CH ₂ OBn	PhCH ₂	(R) -CO ₂ Me
254	H	H	(S)- CH ₂ OH	Fmoc	(S) -CO ₂ Me
255	H	H	(S)- CH ₂ OH	PhCH ₂	(S) -CO ₂ Me
256	H	H	(S)- CH ₂ OBn	Fmoc	(S) -CO ₂ Me
257	H	H	(S)- CH ₂ OBn	PhCH ₂	(S) -CO ₂ Me
258	H	H	(S)- CH ₂ OH	Fmoc	(R) -CO ₂ Me
259	H	H	(S)- CH ₂ OH	PhCH ₂	(R) -CO ₂ Me
260	H	H	(S)- CH ₂ OBn	Fmoc	(R) -CO ₂ Me
261	H	H	(S)- CH ₂ OBn	PhCH ₂	(R) -CO ₂ Me
262	H	H	(S)-CH ₂ CH(Me) ₂	Bn	(R) -CO ₂ Me
263	H	H	(R)-CH ₂ CH(Me) ₂	Bn	(R) -CO ₂ Me
264	H	H	(S)-CH ₂ CH(Me) ₂	Bn	(S) -CO ₂ Me
265	H	H	(R)-CH ₂ CH(Me) ₂	Bn	(S) -CO ₂ Me
266	H	H	(S)-CH ₂ CH(Me) ₂	Fmoc	(R) -CO ₂ Me
267	H	H	(R)-CH ₂ CH(Me) ₂	Fmoc	(R) -CO ₂ Me
268	H	H	(S)-CH ₂ CH(Me) ₂	Fmoc	(S) -CO ₂ Me

269	H	H	(R)-CH ₂ CH(Me) ₂	Fmoc	(S) -CO ₂ Me
270	H	H	(S)-Me	H	(R) -CH ₂ OH
271	H	H	(S)-Me	Bn	(R) -CH ₂ OH
272	H	H	(S)-Me	Fmoc	(R) -CH ₂ OH
273	H	H	(R)-Me	H	(R) -CH ₂ OH
274	H	H	(R)-Me	Bn	(R) -CH ₂ OH
275	H	H	(R)-Me	Fmoc	(R) -CH ₂ OH
276	H	H	(S)-Me	H	(S) -CH ₂ OH
277	H	H	(S)-Me	Bn	(S) -CH ₂ OH
278	H	H	(S)-Me	Fmoc	(S) -CH ₂ OH
279	H	H	(R)-Me	H	(S) -CH ₂ OH
280	H	H	(R)-Me	Bn	(S) -CH ₂ OH
281	H	H	(R)-Me	Fmoc	(S) -CH ₂ OH
282	H	H	(S)-CH ₂ CH(Me) ₂	H	(R) -CH ₂ OH
283	H	H	(S)-CH ₂ CH(Me) ₂	Bn	(R) -CH ₂ OH
284	H	H	(S)-CH ₂ CH(Me) ₂	Fmoc	(R) -CH ₂ OH
285	H	H	(R)-CH ₂ CH(Me) ₂	H	(R) -CH ₂ OH
286	H	H	(R)-CH ₂ CH(Me) ₂	Bn	(R) -CH ₂ OH
287	H	H	(R)-CH ₂ CH(Me) ₂	Fmoc	(R) -CH ₂ OH
288	H	H	(S)-CH ₂ CH(Me) ₂	H	(S) -CH ₂ OH
289	H	H	(S)-CH ₂ CH(Me) ₂	Bn	(S) -CH ₂ OH
290	H	H	(S)-CH ₂ CH(Me) ₂	Fmoc	(S) -CH ₂ OH
291	H	H	(R)-CH ₂ CH(Me) ₂	H	(S) -CH ₂ OH
292	H	H	(R)-CH ₂ CH(Me) ₂	Bn	(S) -CH ₂ OH
293	H	H	(R)-CH ₂ CH(Me) ₂	Fmoc	(S) -CH ₂ OH
294	H	H	(S) -PhCH ₂	H	(R) -CH ₂ OH
295	H	H	(S) -PhCH ₂	Bn	(R) -CH ₂ OH
296	H	H	(S) -PhCH ₂	Fmoc	(R) -CH ₂ OH
297	H	H	(R) -PhCH ₂	H	(R) -CH ₂ OH
298	H	H	(R) -PhCH ₂	Bn	(R) -CH ₂ OH
299	H	H	(R) -PhCH ₂	Fmoc	(R) -CH ₂ OH

300	H	H	(S)-PhCH ₂	H	(S)-CH ₂ OH
301	H	H	(S)-PhCH ₂	Bn	(S)-CH ₂ OH
302	H	H	(S)-PhCH ₂	Fmoc	(S)-CH ₂ OH
303	H	H	(R)-PhCH ₂	H	(S)-CH ₂ OH
304	H	H	(R)-PhCH ₂	Bn	(S)-CH ₂ OH
305	H	H	(R)-PhCH ₂	Fmoc	(S)-CH ₂ OH
306	H	H	(R)-CH ₂ OH	Fmoc	(S)-CH ₂ OH
307	H	H	(R)-CH ₂ OH	PhCH ₂	(S)-CH ₂ OH
308	H	H	(R)-CH ₂ OBN	Fmoc	(S)-CH ₂ OH
309	H	H	(R)-CH ₂ OBN	PhCH ₂	(S)-CH ₂ OH
310	H	H	(R)-CH ₂ OH	Fmoc	(R)-CH ₂ OH
311	H	H	(R)-CH ₂ OH	PhCH ₂	(R)-CH ₂ OH
312	H	H	(R)-CH ₂ OBN	Fmoc	(R)-CH ₂ OH
313	H	H	(R)-CH ₂ OBN	PhCH ₂	(R)-CH ₂ OH
314	H	H	(S)-CH ₂ OH	Fmoc	(S)-CH ₂ OH
315	H	H	(S)-CH ₂ OH	PhCH ₂	(S)-CH ₂ OH
316	H	H	(S)-CH ₂ OBN	Fmoc	(S)-CH ₂ OH
317	H	H	(S)-CH ₂ OBN	PhCH ₂	(S)-CH ₂ OH
318	H	H	(S)-CH ₂ OH	Fmoc	(R)-CH ₂ OH
319	H	H	(S)-CH ₂ OH	PhCH ₂	(R)-CH ₂ OH
320	H	H	(S)-CH ₂ OBN	Fmoc	(R)-CH ₂ OH
321	H	H	(S)-CH ₂ OBN	PhCH ₂	(R)-CH ₂ OH

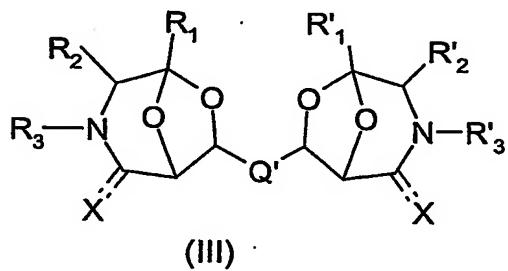


Compound	R ₁	R ₂	R ₃	R' ₁	R' ₂	R ₆
322	H	H	H	H	H	CO ₂ Me
323	H	H	H	H	H	CONHMe

324	H	H	PhCH ₂	H	H	CO ₂ Me
325	H	H	PhCH ₂	H	H	CONHMe
326	H	H	Fmoc	H	H	CO ₂ Me
327	H	H	Fmoc	H	H	CONHMe
328	H	H	Boc	H	H	CO ₂ Me
329	H	H	Boc	H	H	CONHMe
330	H	PhCH ₂	H	H	H	CO ₂ Me
331	H	PhCH ₂	H	H	H	CONHMe
332	H	PhCH ₂	PhCH ₂	H	H	CO ₂ Me
333	H	PhCH ₂	PhCH ₂	H	H	CONHMe
334	H	PhCH ₂	Fmoc	H	H	CO ₂ Me
335	H	PhCH ₂	Fmoc	H	H	CONHMe
336	H	PhCH ₂	Boc	H	H	CO ₂ Me
337	H	PhCH ₂	Boc	H	H	CONHMe
338	H	H	H	H	PhCH ₂	CO ₂ Me
339	H	H	H	H	PhCH ₂	CONHMe
340	H	H	PhCH ₂	H	PhCH ₂	CO ₂ Me
341	H	H	PhCH ₂	H	PhCH ₂	CONHMe
342	H	H	Fmoc	H	PhCH ₂	CO ₂ Me
343	H	H	Fmoc	H	PhCH ₂	CONHMe
344	H	H	Boc	H	PhCH ₂	CO ₂ Me
345	H	H	Boc	H	PhCH ₂	CONHMe
346	H	PhCH ₂	H	H	PhCH ₂	CO ₂ Me
347	H	PhCH ₂	H	H	PhCH ₂	CONHMe
348	H	PhCH ₂	PhCH ₂	H	PhCH ₂	CO ₂ Me
349	H	PhCH ₂	PhCH ₂	H	PhCH ₂	CONHMe
350	H	PhCH ₂	Fmoc	H	PhCH ₂	CO ₂ Me
351	H	PhCH ₂	Fmoc	H	PhCH ₂	CONHMe
352	H	PhCH ₂	Boc	H	PhCH ₂	CO ₂ Me
353	H	PhCH ₂	Boc	H	PhCH ₂	CONHMe
354	Ph	H	H	H	H	CO ₂ Me

355	Ph	H	H	H	H	CONHMe
356	Ph	H	PhCH ₂	H	H	CO ₂ Me
357	Ph	H	PhCH ₂	H	H	CONHMe
358	Ph	H	Fmoc	H	H	CO ₂ Me
359	Ph	H	Fmoc	H	H	CONHMe
360	Ph	H	Boc	H	H	CO ₂ Me
361	Ph	H	Boc	H	H	CONHMe
362	H	H	H	Ph	H	CO ₂ Me
363	H	H	H	Ph	H	CONHMe
364	H	H	PhCH ₂	Ph	H	CO ₂ Me
365	H	H	PhCH ₂	Ph	H	CONHMe
366	H	H	Fmoc	Ph	H	CO ₂ Me
367	H	H	Fmoc	Ph	H	CONHMe
368	H	H	Boc	Ph	H	CO ₂ Me
369	H	H	Boc	Ph	H	CONHMe
370	Ph	H	H	Ph	H	CO ₂ Me
371	Ph	H	H	Ph	H	CONHMe
372	Ph	H	PhCH ₂	Ph	H	CO ₂ Me
373	Ph	H	PhCH ₂	Ph	H	CONHMe
374	Ph	H	Fmoc	Ph	H	CO ₂ Me
375	Ph	H	Fmoc	Ph	H	CONHMe
376	Ph	H	Boc	Ph	H	CO ₂ Me
377	Ph	H	Boc	Ph	H	CONHMe
378	H	H	H	H	CH ₂ OH	CO ₂ Me
379	H	H	H	H	CH ₂ OH	CONHMe
380	H	H	PhCH ₂	H	CH ₂ OH	CO ₂ Me
381	H	H	PhCH ₂	H	CH ₂ OH	CONHMe
382	H	H	Fmoc	H	CH ₂ OH	CO ₂ Me
383	H	H	Fmoc	H	CH ₂ OH	CONHMe
384	H	H	Boc	H	CH ₂ OH	CO ₂ Me
385	H	H	Boc	H	CH ₂ OH	CONHMe

386	H	PhCH ₂	H	H	CH ₂ OH	CO ₂ Me
387	H	PhCH ₂	H	H	CH ₂ OH	CONHMe
388	H	PhCH ₂	PhCH ₂	H	CH ₂ OH	CO ₂ Me
389	H	PhCH ₂	PhCH ₂	H	CH ₂ OH	CONHMe
390	H	PhCH ₂	Fmoc	H	CH ₂ OH	CO ₂ Me
391	H	PhCH ₂	Fmoc	H	CH ₂ OH	CONHMe
392	H	PhCH ₂	Boc	H	CH ₂ OH	CO ₂ Me
393	H	PhCH ₂	Boc	H	CH ₂ OH	CONHMe
394	Ph	H	H	H	CH ₂ OH	CO ₂ Me
395	Ph	H	H	H	CH ₂ OH	CONHMe
396	Ph	H	PhCH ₂	H	CH ₂ OH	CO ₂ Me
397	Ph	H	PhCH ₂	H	CH ₂ OH	CONHMe
398	Ph	H	Fmoc	H	CH ₂ OH	CO ₂ Me
399	Ph	H	Fmoc	H	CH ₂ OH	CONHMe
400	Ph	H	Boc	H	CH ₂ OH	CO ₂ Me
401	Ph	H	Boc	H	CH ₂ OH	CONHMe



Compound	R ₁	R ₂	R ₃	R' ₁	R' ₂	R ₃	X	Q'
402	H	H	H	H	H	H	O	CO-NH(CH ₂) ₂ NH-CO
403	H	H	H	H	H	H	O	CO-NH(CH ₂) ₄ NH-CO
404	H	H	H	H	H	H	O	CO-NH(CH ₂) ₆ NH-CO
405	H	H	H	H	H	H	O	CO-N(C ₂ H ₄)N-CO
406	H	H	PhCH ₂	H	H	PhCH ₂	O	CO-NH(CH ₂) ₂ NH-CO
407	H	H	PhCH ₂	H	H	PhCH ₂	O	CO-NH(CH ₂) ₄ NH-CO
408	H	H	PhCH ₂	H	H	PhCH ₂	O	CO-NH(CH ₂) ₆ NH-CO

409	H	H	PhCH ₂	H	H	PhCH ₂	O	CO-N(C ₂ H ₄)N-CO
410	H	H	PhCH ₂	H	H	PhCH ₂	H	CO-NH(CH ₂) ₂ NH-CO
411	H	H	PhCH ₂	H	H	PhCH ₂	H	CO-NH(CH ₂) ₄ NH-CO
412	H	H	PhCH ₂	H	H	PhCH ₂	H	CO-NH(CH ₂) ₆ NH-CO
413	H	H	PhCH ₂	H	H	PhCH ₂	H	CO-N(C ₂ H ₄)N-CO
414	H	PhCH ₂	PhCH ₂	H	PhCH ₂	PhCH ₂	O	CO-NH(CH ₂) ₂ NH-CO
415	H	PhCH ₂	PhCH ₂	H	PhCH ₂	PhCH ₂	O	CO-NH(CH ₂) ₄ NH-CO
416	H	PhCH ₂	PhCH ₂	H	PhCH ₂	PhCH ₂	O	CO-NH(CH ₂) ₆ NH-CO
417	H	PhCH ₂	PhCH ₂	H	PhCH ₂	PhCH ₂	O	CO-N(C ₂ H ₄)N-CO
418	H	PhCH ₂	PhCH ₂	H	PhCH ₂	PhCH ₂	H	CO-NH(CH ₂) ₂ NH-CO
419	H	PhCH ₂	PhCH ₂	H	PhCH ₂	PhCH ₂	H	CO-NH(CH ₂) ₄ NH-CO
420	H	PhCH ₂	PhCH ₂	H	PhCH ₂	PhCH ₂	H	CO-NH(CH ₂) ₆ NH-CO
421	H	PhCH ₂	PhCH ₂	H	PhCH ₂	PhCH ₂	H	CO-N(C ₂ H ₄)N-CO
422	Ph	H	PhCH ₂	Ph	H	PhCH ₂	O	CO-NH(CH ₂) ₂ NH-CO
423	Ph	H	PhCH ₂	Ph	H	PhCH ₂	O	CO-NH(CH ₂) ₄ NH-CO
424	Ph	H	PhCH ₂	Ph	H	PhCH ₂	O	CO-NH(CH ₂) ₆ NH-CO
425	Ph	H	PhCH ₂	Ph	H	PhCH ₂	O	CO-N(C ₂ H ₄)N-CO
426	Ph	H	PhCH ₂	Ph	H	PhCH ₂	H	CO-NH(CH ₂) ₂ NH-CO
427	Ph	H	PhCH ₂	Ph	H	PhCH ₂	H	CO-NH(CH ₂) ₄ NH-CO
428	Ph	H	PhCH ₂	Ph	H	PhCH ₂	H	CO-NH(CH ₂) ₆ NH-CO
429	Ph	H	PhCH ₂	Ph	H	PhCH ₂	H	CO-N(C ₂ H ₄)N-CO
430	Ph	H	PhCH ₂	Ph	H	PhCH ₂	H	CO-NH(CH ₂) ₂ NH-CO
431	Ph	H	PhCH ₂	Ph	H	PhCH ₂	H	CO-NH(CH ₂) ₄ NH-CO
432	Ph	H	PhCH ₂	Ph	H	PhCH ₂	H	CO-NH(CH ₂) ₆ NH-CO
433	Ph	H	PhCH ₂	Ph	H	PhCH ₂	H	CO-N(C ₂ H ₄)N-CO
434	Ph	H	Ph	Ph	H	Ph	O	CO-NH(CH ₂) ₂ NH-CO
435	Ph	H	Ph	Ph	H	Ph	O	CO-NH(CH ₂) ₄ NH-CO
436	Ph	H	Ph	Ph	H	Ph	O	CO-NH(CH ₂) ₆ NH-CO
437	Ph	H	Ph	Ph	H	Ph	O	CO-N(C ₂ H ₄)N-CO
438	NO ₂ -Ph	H	Ph	NO ₂ -Ph	H	Ph	O	CO-NH(CH ₂) ₂ NH-CO
439	NO ₂ -Ph	H	Ph	NO ₂ -Ph	H	Ph	O	CO-NH(CH ₂) ₃ NH-CO

440	NO ₂ -Ph	H	Ph	NO ₂ -Ph	H	Ph	O	CO-NH(CH ₂) ₄ NH-CO
441	NO ₂ -Ph	H	Ph	NO ₂ -Ph	H	Ph	O	CO-NH(CH ₂) ₅ NH-CO
442	NO ₂ -Ph	H	Ph	NO ₂ -Ph	H	Ph	O	CO-NH(CH ₂) ₆ NH-CO
443	NO ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	O	CO-N(C ₂ H ₄)N-CO
444	NH ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	O	CO-NH(CH ₂) ₂ NH-CO
445	NH ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	O	CO-NH(CH ₂) ₃ NH-CO
446	NH ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	O	CO-NH(CH ₂) ₄ NH-CO
447	NH ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	O	CO-NH(CH ₂) ₅ NH-CO
448	NH ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	O	CO-NH(CH ₂) ₆ NH-CO
449	NH ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	O	CO-N(C ₂ H ₄)N-CO
450	NO ₂ -Ph	H	Ph	NO ₂ -Ph	H	Ph	H	CO-NH(CH ₂) ₂ NH-CO
451	NO ₂ -Ph	H	Ph	NO ₂ -Ph	H	Ph	H	CO-NH(CH ₂) ₃ NH-CO
452	NO ₂ -Ph	H	Ph	NO ₂ -Ph	H	Ph	H	CO-NH(CH ₂) ₄ NH-CO
453	NO ₂ -Ph	H	Ph	NO ₂ -Ph	H	Ph	H	CO-NH(CH ₂) ₅ NH-CO
454	NO ₂ -Ph	H	Ph	NO ₂ -Ph	H	Ph	H	CO-NH(CH ₂) ₆ NH-CO
455	NO ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	H	CO-N(C ₂ H ₄)N-CO
456	NH ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	H	CO-NH(CH ₂) ₂ NH-CO
457	NH ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	H	CO-NH(CH ₂) ₃ NH-CO
458	NH ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	H	CO-NH(CH ₂) ₄ NH-CO
459	NH ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	H	CO-NH(CH ₂) ₅ NH-CO
460	NH ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	H	CO-NH(CH ₂) ₆ NH-CO
461	NH ₂ -Ph	H	Ph	NH ₂ -Ph	H	Ph	H	CO-N(C ₂ H ₄)N-CO

5. The pharmaceutical composition according to claims 1-4, further comprising pharmaceutically acceptable excipients and/or diluents.

6. Use of 3-aza-bicyclo[3.2.1]octane derivatives of formula (I), their dimers of formula (II) or (III), and mixtures thereof as defined in claims 1-4, for the preparation of pharmaceutical compositions for the treatment of:

5 i) neurodegenerative, inflammatory, toxic, traumatic, or vascular disorders of the central, peripheral, or autonomic nervous system, neural damages secondary to hypoxia, ischaemia, burns, chemotherapy, toxic compounds of various origin

10 (including alcohol), infections, trauma (including surgical trauma) originating

axotomy of motoneurons, sensorial, motor, or sensorimotor neuropathies, or autonomic dysfunctions secondary to diverse pathologies, genetic disorders, nervous pathologies of diverse origin, some ocular pathologies, corneal diseases of diverse origin, pathologies from reduced motility of the gastro-intestinal tract or

5 from urinary bladder atony, endocrine neoplastic pathologies, clinical conditions in which stimulation of learning processes is advantageous, and all pathological conditions originating from apoptotic processes of neural cells;

ii) acquired immunodeficiency diseases due to reduced or absent bioavailability of NGF;

10 iii) conditions in which stimulation of neoangiogenesis may be advantageous;

iv) certain ocular pathologies.

7. Use of 3-aza-bicyclo[3.2.1]octane derivatives of formula (I), their dimers of formula (II) or (III) and mixtures thereof according to claim 6, in which said neurodegenerative, inflammatory, toxic, traumatic, or vascular disorders of the 15 central, peripheral, or autonomic nervous system are selected from Alzheimer Disease (AD), Amyotrophic Lateral Sclerosis (ALS), Huntington disease, multiple sclerosis, epilepsy, Down syndrome, nervous deafness and Ménière's disease.

8. Use of 3-aza-bicyclo[3.2.1]octane derivatives of formula (I), their dimers of formula (II) or (III) and mixtures thereof according to claim 6, in which said neural 20 damages secondary to infections are selected from polio and HIV virus.

9. Use of 3-aza-bicyclo[3.2.1]octane derivatives of formula (I), their dimers of formula (II) or (III) and mixtures thereof according to claim 6, in which said genetic disorders are selected from Charcot-Marie-Tooth disease, Refsum disease, 25 abetalipoproteinemia, Tangier disease, Krabbe disease, metachromatic leukodystrophy, Fabry disease, Dejerine-Sottas disease.

10. Use of 3-aza-bicyclo[3.2.1]octane derivatives of formula (I), their dimers of formula (II) or (III) and mixtures thereof according to claim 6, in which said nervous pathologies of diverse origin are selected from diffuse atrophy of cerebral cortex, Lewy body dementia, Pick's disease, mesolimbocortical dementia, neuronal ceroid 30 lipofuscinosis, thalamic degeneration, cortico-striatal-spinal degeneration, cortico-basal ganglionic degeneration, cerebro-cerebellar degeneration, familial dementia with spastic paraparesis, polyglucosan bodies disease, Shy-Drager syndrome,

olivopontocerebellar atrophy, progressive supranuclear palsy, deforming muscular dystony, Hallervorden-Spatz disease, Meige's syndrome, familial shivering, Gilles de la Tourette syndrome, chorea-acanthocytosis syndrome, Friedreich's ataxia, Holmes' corticocerebellar familial atrophy, Gerstmann-Straussler-Scheinker disease, progressive spinal muscular atrophy, spastic paraplegia, peroneal muscular atrophy, hypertrophic interstitial polyneuropathy and polyneuritic ataxic heredopathy.

5 11. Use of 3-aza-bicyclo[3.2.1]octane derivatives of formula (I), their dimers of formula (II) or (III) and mixtures thereof according to claim 6, in which said ocular pathologies are selected from optic nerve neuropathies, retinal degeneration, 10 ophtalmoplegy and glaucoma; and said corneal diseases of diverse origin are selected from neurotrophic ulcers, post-traumatic and post-infective corneal disorders.

15 12. Use of 3-aza-bicyclo[3.2.1]octane derivatives of formula (I), their dimers of formula (II) or (III) and mixtures thereof according to claim 6, in which said pathologies from reduced motility of the gastro-intestinal tract or from urinary bladder atony are selected from interstitial cystitis and diabetic cystitis.

20 13. Use of 3-aza-bicyclo[3.2.1]octane derivatives of formula (I), their dimers of formula (II) or (III) and mixtures thereof according to claim 6, in which said conditions in which stimulation of neoangiogenesis may be advantageous are selected from myocardial infarction, stroke, cerebral aneurysms, gastro-duodenal 25 ulcers, wound healing and peripheral vasculopathies.

14. Use of 3-aza-bicyclo[3.2.1]octane derivatives of formula (I), their dimers of formula (II) or (III) and mixtures thereof according to claim 6, in which said 25 acquired immunodeficiency disease is immunodeficiency of ageing.

15. Use of 3-aza-bicyclo[3.2.1]octane derivatives of formula (I), their dimers of formula (II) or (III) and mixtures thereof as defined in claims 1-4, as reagents for promoting growth and/or *in vivo*, *in vitro* or *ex vivo* survival of neuronal cells.

30 16. Use of 3-aza-bicyclo[3.2.1]octane derivatives of formula (I), their dimers of formula (II) or (III), and mixtures thereof according to claim 15, wherein said neural cells are selected from the group consisting of dopaminergic, cholinergic, sensorial neurons, striatal cells, cortical cells, cells of the corpus striatum, hippocampus,

cerebellum, olfactory bulbs, peri-aqueductal cells, cells of the raphe nuclei, of the locus coeruleus, of the dorsal root ganglia, sympathetic neurons, lower motoneurons, nervous stem cells, and cells anyhow deriving from the neural plaque.

- 5 17. Use of 3-aza-bicyclo[3.2.1]octane derivatives of formula (I), their dimers of formula (II) or (III), and mixtures thereof as defined in claims 1-4, for the preparation of culture and storage media useful for conservation of explanted corneas destined to transplantation.
- 10 18. Use of 3-aza-bicyclo[3.2.1]octane derivatives of formula (I), their dimers of formula (II) or (III), and mixtures thereof as defined in claims 1-4, labelled with suitable reagents (contrast agents, radioisotopes, fluorescent agents etc.); and possibly processed with procedures useful for medical imaging purposes, in the imaging analysis of tissues and organs containing neurotrophine receptors.
- 15 19. Use of 3-aza-bicyclo[3.2.1]octane derivatives of formula (I), their dimers of formula (II) or (III), and mixtures thereof according to claim 18, for monitoring the use and efficacy of drugs or for the diagnosis of mammal diseases in which the neurotrophine receptors are involved.
- 20 20. The 3-aza-bicyclo[3.2.1]octane derivatives of formula (I) and their dimers of formula (II) and (III) as defined in claim 1, with the exclusion of the compounds indicated by the following numbers:
1,2,5,7,8,9,10,12,13,17,19,20,21,32,34,35,36,38,40,44,45,48,58,60,64,65,66,70,75,76,
77,78,79,83,87,91,95,99,101,103,138,145,152,154,163,164,168,172,174,176,178,
184,186,192,322,324,
and as defined in claim 4.
- 25 21. The 3-aza-bicyclo[3.2.1]octane derivatives of formula (I) and their dimers of formula (II) and (III) according to claim 20, selected from the compounds indicated by the following numbers:
3,4,6,11,14-16,18,22-31,33,37,39,41-43,45-57,59,61-63,67-69,71-74,80-82,84-
86,88-90,92-94,96-98,100,102,104-137,139-144,146-151,153,155-162,165-
30 167,169-171,173,175,177,179-183,185,187-191,193-321,323,325-461,
and as defined in claim 4.

Figure 1

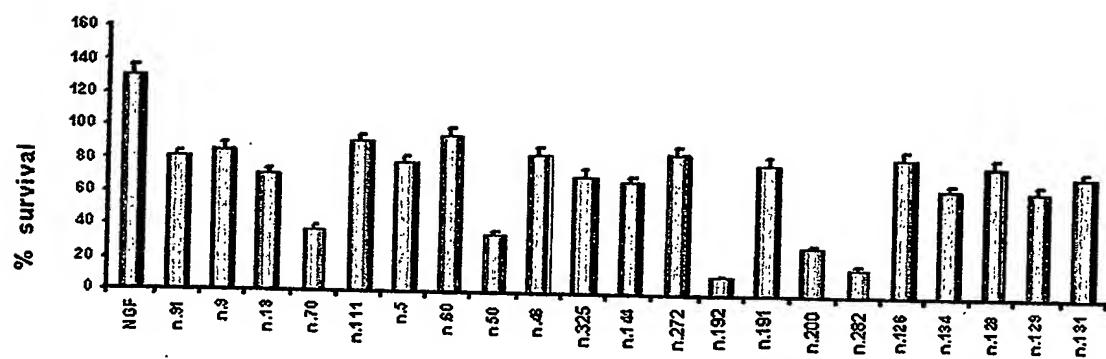


Figure 2

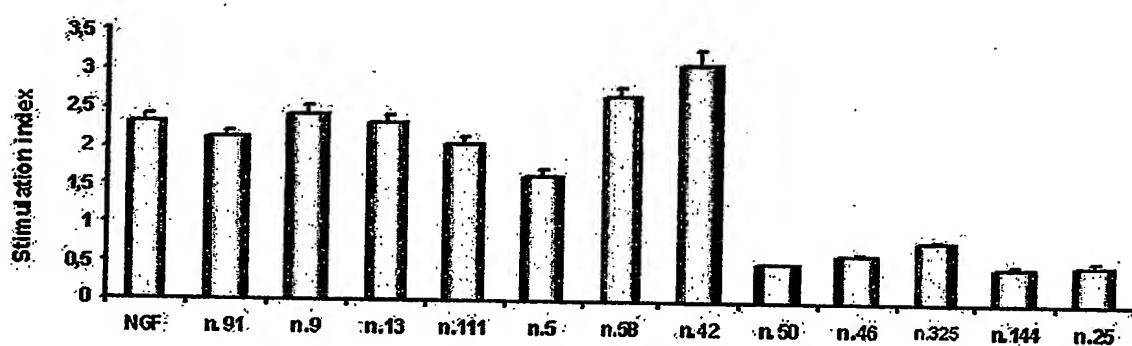


Figure 3

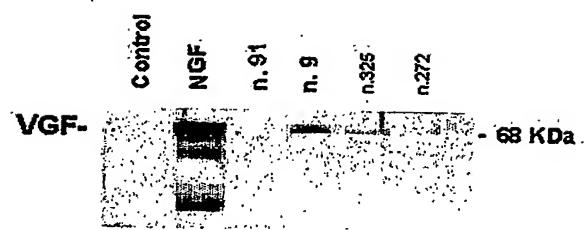


Figure 4a

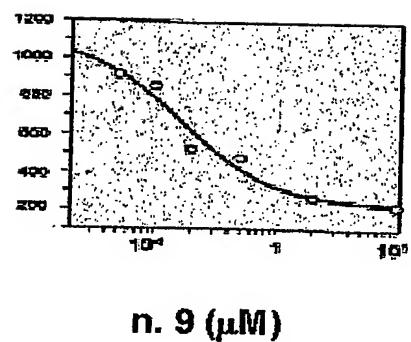
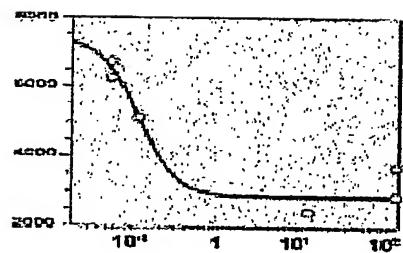


Figure 4b



NGF (nM)

Figure 5

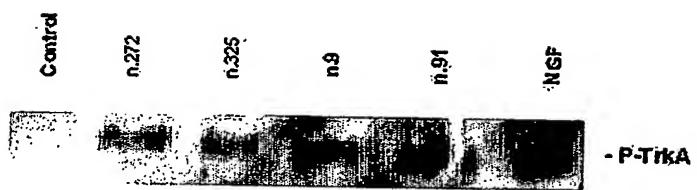
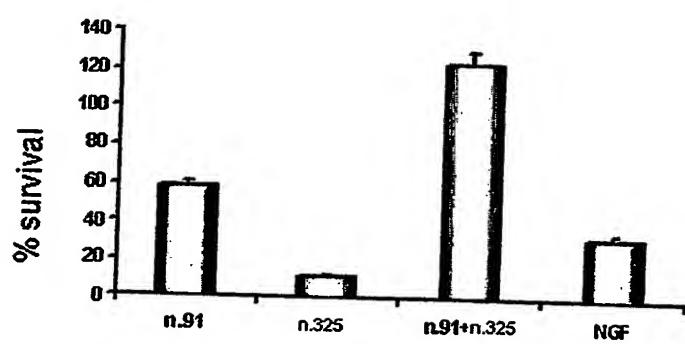


Figure 6



INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 03/06471

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/55 A61K31/551 A61K31/553 A61K31/554

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category ^o	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>MAY, M. ET AL.: "Cholinomimetic Activities of Some Analogs of cis-2-Methyl-4-dimethylaminomethyl-1,3-dioxolane Methiodide" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 57, no. 3, 1968, pages 511-513, XP008024001 abstract</p> <p>---</p> <p>-/-</p>	1-21

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the International search	Date of mailing of the International search report
11 November 2003	26/11/2003
Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beyss, E

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 03/06471

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>GUARNA, A. ET AL.: "Synthesis and Reactivity of Bicycles Derived from Tartaric Acid and alpha-Amino Acids: A Novel Class of Conformationally Constrained Dipeptide Isosteres Based upon Enantiopure 3-Aza-6,8-dioxabicyclo[3.2.1.]octane-7-carboxylic Acid"</p> <p>JOURNAL OF ORGANIC CHEMISTRY, vol. 64, 14 September 1999 (1999-09-14), pages 7347-7364, XP002260506 examples; table 1</p> <p>-----</p>	20
A	<p>MACHETTI, F. ET AL.: "Oligomers of Enantiopure Bicyclic gamma/delta-Amino Acids (BTAA). 1. Synthesis and Conformational Analysis of 3-Aza-6,8-dioxabicyclo[3.2.1.]octane-7-carboxylic Acid Oligomers (PolyBTG)"</p> <p>ORGANIC LETTERS, vol. 2, no. 25, 11 November 2000 (2000-11-11), pages 3987-3990, XP002260507 abstract</p> <p>-----</p>	21

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/EP 03/06471**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 15 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

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